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ESOPHAGITIS AFTER ESOPHAGOGASTRIC ANASTOMOSIS

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AS A consequence of scientific developments which make major intrathoracic surgery not only feasible but safe, the surgeon can now remove or short-circuit the esophagogastric junction in the treatment of certain lesions. By such operations he removes or disturbs a group of structures which include the cardiac sphincter, cardiac valve, and diaphragmatic pinchcock known collectively as the cardiac mechanism. Their prime function is to insure unidirectional transit from the esophagus into the stomach.[28, 32]

That disturbed function of the cardiac mechanism is undesirable has been postulated by several investigators[4, 7, 30, 47] who observed considerable postoperative disability in persons subjected to cardioplasty or esophagogastrostomy for obstructing lesions at the esophagogastric junction. Although soon after operation patients were relieved of esophageal obstruction, after a latent period there appeared progressive dysphagia and difficulty in alimentation. Mild regurgitation which was initially troublesome soon was accompanied by substernal burning, dysphagia, pain on swallowing, failure to gain weight, and occasional hematemesis. Reappearance of esophageal obstruction often provoked fear that the primary disease was recurring. However, many times this proved not to be the case and it was shown that the individual suffered from chronic peptic esophagitis as a result of irritation by corrosive gastric juice.

Surgical procedures which destroy or by-pass the cardiac mechanism allow repeated regurgitation of gastric juice into the esophagus.[2, 15, 17, 26, 36] A plethora of experimental[5, 36, 39, 44] and clinical evidence[7, 15, 20, 24, 34, 39-41] demonstrates that normal gastric juice in such circumstances will initiate disabling esophagitis. The tendency is even more marked in association with the hypersecretion and hyperacidity of gastric and duodenal ulcer.[13, 16, 23-25, 29, 40-43, 45, 48, 49]

Allison[1, 2] and many others[9, 10, 12, 14, 15, 18, 21, 22, 25, 27, 33-35, 38, 40, 41, 45, 47] directed attention to this relationship in esophageal hiatal hernia. More recently Barrett and Franklin,[7] and Allison and Borrie[4] described the appearance of

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peptic esophagitis following esophagogastric anastomosis for conditions both malignant and benign. Although there has been casual affirmation in this country of the consequences of esophagogastrostomy, the increasing frequency with which these operations are being employed makes careful analysis imperative.

In order to determine the seriousness of esophagitis following operations on the esophagogastric junction, the records of all patients who underwent esophagogastrostomy or cardioplasty at the Mayo Clinic over a sixteen-year period (1935 through 1950) were studied and certain data thereby derived were analyzed.

MATERIAL AND METHODS

The records of 169 patients who had undergone esophagogastrostomy or cardioplasty at the clinic were collected (Table I). The sixteen-year period of 1935 through 1950 was selected as it was during this interval that such operations were employed with increasing frequency. By examination, in addition, of all records in which a primary diagnosis of esophagitis was established during the same period, several cases were collected wherein esophagitis developed after esophagogastric operations performed elsewhere.

TABLE I. CASES CONSIDERED

	CASES
Esophagogastrostomy or cardioplasty (1935 through 1950)	169
Esophagitis (1935 through 1950)	111
Total	280
Deleted (see text)	215
For study	65

Most of the patients had undergone esophagogastrostomy following esophagogastric resection for obstructing lesions in the gastric cardia and esophagus. The primary diagnosis in the majority of these cases was carcinoma, although there were a few cases of cardiospasm and other benign conditions. In the remainder of the cases of intractable cardiospasm, treatment had consisted of one or another type of cardioplasty.

Eliminated from the study were those cases in which follow-up was considered inadequate because of death within a month of the operation or death elsewhere without detailed information as to the circumstances. No follow-up data were available in 11 cases. Proved or presumed recurrence of malignant disease interferred with the interpretation of esophageal signs and symptoms and such cases were deleted from the study.

After the above eliminations there remained sixty-five cases suitable for study (Table I). Among these, twenty-nine patients underwent postoperative esophagoscopy, or there was surgical or necropsy tissue available. In the remaining thirty-six cases, although no postoperative esophagoscopy was done, there was sufficient clinical and laboratory information to make a presumptive diagnosis possible.

No case fulfilling the above criteria was eliminated from the present study because the data did not support a diagnosis of esophagitis. However, it may be readily appreciated that because of technical obstacles inherent in a study of this nature, it is impossible from our data to ascertain the proportion of the total patients treated surgically who might eventually have esophagitis.

The present investigation was dichotomized in order to emphasize the greater reliance placed upon the first group of cases in which esophagoscopy was performed or tissue was available for examination. In the second group of cases, however, the data available seemed sufficient to establish or rule out a presumptive diagnosis of esophagitis or stricture.

RESULTS

Group 1.—In the first group of 29 patients in which a definite diagnosis of postoperative esophagitis was made as a result of tissue study or direct observation of the esophagus, the primary diagnosis for which esophagogastric anastomosis was performed is indicated in Table II.

TABLE II. RESULTS OF POSTOPERATIVE ESOPHAGOSCOPY OR TISSUE EXAMINATION OR BOTH AFTER ESOPHAGOGASTROSTOMY OR CARDIOPLASTY (GROUP 1)

PRIMARY DISEASE	POSTOPERATIVE ESOPHAGITIS OR STRICTURE, CASES				
	ESOPHAGITIS	STRICTURE	BOTH	NEITHER	TOTAL
Intractable cardiospasm*	5	1	1		7
Cancer of gastric cardia	7	1	5		13
Cancer of esophagus	2	2		1	5
Esophageal varices (Banti)	1				1
Short esophagus hiatal hernia	1				1
Lye stricture of esophagus		1			1
Leiomyoma of esophagus			1		1
Total	16	5	7	1	29

*In one case an initial Finney cardioplasty was modified six years later by cardioesophageal resection after development of inflammatory esophageal stricture.

TABLE III. OPERATIVE PROCEDURES EMPLOYED IN CASES OF INTRACTABLE CARDIOSPASM

OPERATION	CASES		
	GROUP 1	GROUP 2	TOTAL
Wendel (Heineke-Mikulicz)	2	3	5
Gröndahl (Finney)	3*	2	5
Heller (Zaaijer modification)		3	3
Heyrovsky		4	4
Esophagogastrectomy	1	1	2
Type unidentified	1†		1
Total	7	13	20

*In one case an initial Finney cardioplasty was modified six years later by cardioesophageal resection after development of inflammatory esophageal stricture.

†Operation performed elsewhere.

Table III indicates the type of operative procedure employed in each of seven cases of intractable cardiospasm in which cardioplasty or esophagogastric anastomosis was carried out. After operation every one of these patients had symptoms compatible with severe esophageal disease beginning at intervals of two months up to four years. In nearly all instances the distress was progressive. Symptoms included heartburn, regurgitation often precipitated by as-

sumption of the supine position, dysphagia, burning substernal pain often extending to the back and responding in a greater or lesser degree to ingestion of alkali, sensations of food "sticking" in the gullet, hematemesis which in one case required 100 blood transfusions and in two cases proved fatal, loss of weight, and weakness. Table II indicates the postoperative results in this group with intractable cardiospasm.

Except the cases of cardiospasm, in all the cases in Group 1 the operative procedure was partial esophagectomy and partial gastrectomy with re-establishment of gastrointestinal continuity by an end-to-end or end-to-side esophagogastrostomy. The postoperative symptom-free interval and symptoms were similar to those described above. The results summarized in Table II indicate that among these patients esophagitis, stricture, or both developed in all but one.

One patient treated for cancer of the gastric cardia subsequently had a chronic esophageal peptic ulcer which perforated through the muscularis into the pericardial sac and caused a fatal pericarditis one year after operation (Figs. 1 and 2). An esophageal lye stricture was successfully removed in a 6-year-old boy, only to be followed in four months by stricture formation requiring repeated dilatation. He died from acute intussusception a year after operation, and necropsy revealed recurrent stricture without evidence of esophagitis.

In each case of esophagogastrectomy a presumably complete vagotomy accompanied the operation. In two such patients treated for cancer of the cardia the results of preoperative and postoperative gastric analyses after a test meal were available. The concentration of total hydrochloric acid, in clinical units, decreased from 38 to 12 in one case, while in the other case the postoperative value was 16, the preoperative value being undetermined. The concentration of free hydrochloric acid decreased from 28 clinical units before operation to 0 after operation in the first case, while both the preoperative and postoperative values were 0 in the second case. In spite of the absence of free hydrochloric acid, these two patients suffered from postoperative ulcerative esophagitis.

In general, the esophageal symptoms in the cases in Group 1 became progressively more severe after a postoperative symptom-free interval ranging from several days to four years. Ordinarily the symptoms develop within a few months of operation and, nearly always in less than a year. Of the twenty-nine cases in Group 1, esophagitis or stricture or both developed in twenty-eight. Apparently the technical details of esophagogastrostomy or cardioplasty are unimportant, the cardinal factor being a disturbance of normal cardioesophageal closure.

Group 2.—In the second group of 36 postoperative patients in which esophagoscopy or tissue examination was not done, but in which adequate data were available, the primary diagnosis for which esophagogastric anastomosis or cardioplasty was performed is indicated in Table IV. The follow-up period ranged from three months to nine years, with an average of four years.

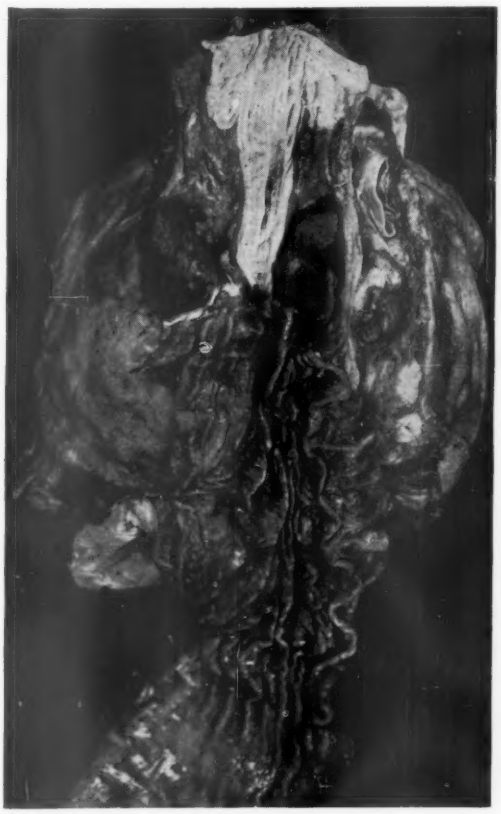

Fig. 1.—Necropsy specimen in a case of cancer of the gastric cardia treated a year previously by esophagogastrectomy. Viewed from the posterior aspect, the white esophagus may be seen to join the stomach where a perforating esophageal ulcer enters the pericardial sac. The patient died from suppurative pericarditis.

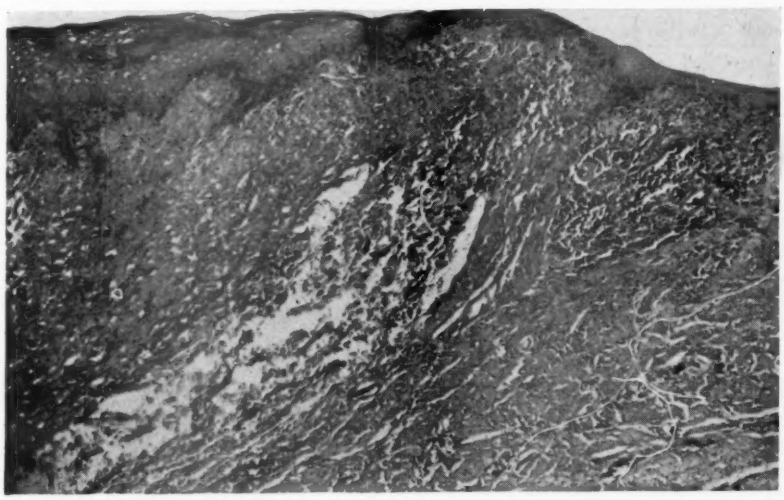

Fig. 2.—Section from the same specimen as in Fig. 1 showing border of the esophageal peptic ulcer. The stratified squamous epithelium has undergone slough, and necrotic fibrin overlies inflammatory granulation tissue (hemotoxylin and eosin, ×70).

Table III indicates the type of operative procedure employed in each of thirteen cases of intractable cardiospasm in which cardioplasty or esophagogastric anastomosis was done. As summarized in Table IV, signs and symptoms compatible with peptic esophagitis or formation of stricture developed in four cases. In those so afflicted the symptom-free interval and symptoms were similar to those of Group 1.

Exclusive of the cases of cardiospasm, the operative procedure in the remaining twenty-three cases was the same as that employed in the majority of cases in Group 1. The postoperative results are summarized in Table IV.

TABLE IV. DEVELOPMENT OF PRESUMPTIVE POSTOPERATIVE ESOPHAGITIS OR STRICTURE OR BOTH IN PATIENTS WITH ADEQUATE FOLLOW-UP BUT WITHOUT ESOPHAGOSCOPY OR TISSUE EXAMINATION (GROUP 2)

PRIMARY DISEASE	POSTOPERATIVE ESOPHAGITIS OR STRICTURE, CASES		
	PRESENT	ABSENT	TOTAL
Intractable cardiospasm	4	9	13
Cancer of gastric cardia	5	7	12
Cancer of esophagus	2	4	6
Esophageal varices (Banti)	1		1
Benign gastric ulcer		2	2
Corrosive esophageal stricture		1	1
Leiomyosarcoma of esophagus		1	1
Total	12	24	36

Summarizing the data in Groups 1 and 2, one finds that among those persons who underwent postoperative esophagoscopy or tissue examination, twenty-eight of twenty-nine had positive signs of esophagitis or formation of stricture. Among thirty-six persons not so examined, signs and symptoms of presumptive esophagitis or formation of stricture were found in twelve (Table V).

TABLE V. DEVELOPMENT OF POSTOPERATIVE ESOPHAGITIS OR ESOPHAGEAL STRICTURE OR BOTH FOLLOWING CARDIOPLASTY OR ESOPHAGOGASTRIC ANASTOMOSIS

GROUP	CASES	
	TOTAL	ESOPHAGITIS OR STRICTURE OR BOTH
1	29	28
2	36	12
Total	65	40

COMMENT

In its physiologic activity the stomach is called upon to secrete gastric juice of high enzymatic and acid content. A balance exists in which the gastric chyme digests food substances while at the same time it spares the gastrointestinal lining. That such a mechanism can be disturbed is attested by the frequency with which gastric and duodenal ulceration occurs. Usually the factors resisting necrosis and ulceration of mucous membrane[46] prevail over the corrosive ones and peptic ulceration is absent. In the presence of gastric hypersecretion and hyperacidity protective factors are overwhelmed and ulceration results.[6, 11, 31, 48]

Some investigators champion the relative importance of the vagus nerves in stimulation of gastric secretion and question the ability of a vagotomized

stomach to secrete gastric chyme of sufficient potency to ulcerate the esophagus. Vagal resection interrupts only the cephalic phase of gastric secretion and does not deter the gastric or intestinal phases.[8, 11] That the latter are potent stimulants has been demonstrated by several investigators[5, 36, 44] and confirmed by the severe ulceration seen after total vagectomy in the present study.

The esophagus possesses an unusual sensitivity to gastric ferments. Wangensteen and Leven[47] have stated lucidly that were the stomach contents to leave via the esophagus rather than the duodenum, peptic ulcer of the esophagus would be the commonest ulceration in the body. Normally protected by a competent unidirectional cardiac mechanism at its lower end, the esophageal lumen except for brief inconsequential intervals contains no gastric juice.[37] When subjected to recurrent contact with gastric juice, such as in the presence of obstructive duodenal ulcer, lax cardia, esophageal hiatal hernia and other unphysiologic conditions, the esophagus becomes inflamed, ulcerated, and scarred.

Operative procedures in the region of the esophagogastric junction which short-circuit, remove, or render incompetent the cardiac mechanism result in repeated and prolonged regurgitation. In certain instances this causes inflammation, ulceration, perforation, hemorrhage, or formation of stricture in the esophagus.[3, 4, 7, 19, 30]

Of a series of twenty-six cases of cardiospasm treated surgically, Barrett and Franklin reported development of esophagitis and formation of stricture in nearly all. The postoperative disability was often greater than that experienced with the untreated disease. Allison and Borrie evaluated a series of 121 operable gastroesophageal obstructions. It was found that peptic esophagitis accounted for a significant number of postoperative strictures, even after complete vagal resection which accompanied removal of the lower part of the esophagus and upper end of the stomach.

In the present study we found that postoperative esophagitis developed after each type of cardioplasty or esophageal resection employed in intractable cardiospasm except the Heller operation. Our experience with the latter has, however, been too limited and brief for any conclusions to be drawn.

The results of the present investigation corroborate the opinions expressed previously to the effect that postoperative regurgitation of gastric juice can incite esophageal peptic inflammation. The sequelae create considerable disability in those so affected. Nearly without exception, in those persons having enough postoperative distress to warrant endoscopic examination, ulcerative peptic esophagitis, or stricture, or both existed. It cannot be categorically stated that every anastomotic esophageal stricture results in part from the action of gastric chyme, but the frequent coexistence of the two suggests a relationship.

SUMMARY

Of sixty-five patients who underwent esophagogastrostomy or cardioplasty, twenty-eight subsequently had positive signs and twelve subsequently had presumptive signs of peptic esophagitis or formation of stricture. No conclusions

as to the frequency of these complications can be drawn from these data, because of the mode of selection of cases. The very fact that they occur at all is of utmost importance, and must act as a stimulus to the development of techniques which will tend to prevent them.

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BENIGN STENOSING ESOPHAGITIS ASSOCIATED WITH VOMITING AND INTUBATION

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IN RECENT years there has been increasing interest in benign stenosis of the esophagus. There are many cases which cannot be attributed to an *exogenous* corrosive such as lye. Esophagitis on an *endogenous* corrosive (acid-pepsin) basis has been implicated as a precursor of benign stenosis. Esophagitis per se is frequent but stenosis is not frequent. Probably no one etiological factor will explain all cases of esophagitis or stenosis. The management of established stenosis is in an evolutionary stage. Review of case histories and results may help in establishing etiology and guiding therapy.

ETIOLOGICAL FACTORS

In general there have been three lines of thought regarding the etiology of esophagitis. The theory of infectious origin includes intraluminal infection such as a diphtheritic membrane and extraluminal infection spread by the periesophageal lymphatics from inflammatory foci within the abdomen and thorax. Other cases of esophagitis, ulceration, and rupture have been attributed to neurogenic factors associated with lesions of the brain. Although these two explanations have served in some cases they have been discredited as primary factors in most.

The majority of cases of inflammatory stenosis can be explained by the sequence of esophagitis, ulceration, and stenosis produced by the action of acid-peptic gastric juice in the lower esophagus. According to this concept, irritation of the esophageal mucosa produced by the gastric juice evokes an inflammatory response which, if repeated often enough, progresses to ulceration and scarring with narrowing of the esophageal lumen. The acceptance of such an explanation requires evidence that gastric juice can gain access to the esophagus and, once there, that it will cause damage. This concept has recently been given support by the work of Ferguson and associates[6] and Wangensteen and Leven.[12] Ferguson, using human cadavers and a variety of animals, showed that "contact of acid gastric juice with esophageal mucosa, whether brought about by vomiting, regurgitation, or by direct application, has a very prompt and devastating effect." At the same time the stomachs of living animals were very little affected by gastric juice perfusion. His experiments demonstrate that gastric juice which does not harm the stomach is capable of damaging the esophagus. That reflux of gastric content into the esophagus can and does occur clinically has been established. Robins and Jankelson[10] observed a reflux of barium meal

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from the stomach into the esophagus in 103 patients, 59 of whom had some gastrointestinal pathology such as gall bladder disease or peptic ulcer. It is significant that the barium often filled the lower third but was never noted to fill the entire esophagus. Burnham[4] found reflux of barium in cases of pylorospasm associated with gall bladder disease.

It might be expected that esophagitis and stenosis would be associated with conditions which allow frequent contact of gastric juice with the lower esophagus. Such association with diseases of the digestive organs which produce vomiting and eructation has been found. In 213 cases of esophagitis found at autopsy[5] there was a history of vomiting, passage of stomach tube, or both, in 46 per cent. In twenty per cent of the cases there was peptic ulcer; in 23 per cent, chronic cholecystitis. In 60 reported cases[3] of benign stricture of the esophagus, 20 patients also had duodenal ulcer and 7 gave a history of gall bladder disease. The causal relationship of chronic esophagitis to shortening of the esophagus has been emphasized by Olsen.[9]

There is no agreement on the mechanism which maintains competence at the esophagogastric juncture, permitting entrance, but not exit, of solids and liquids. Allison[1] has stressed that symptoms of the sliding esophageal hernia are due to esophagitis from gastric juice reflux. He demonstrated both the reflux and the inflammation of the esophagus. According to him cardioesophageal continence is maintained by two mechanisms. The right crus of the diaphragm acts as an external sphincter compressing the walls of the esophagus from side to side and increasing the angle of the esophagus during contraction of the diaphragm. The oblique entrance of the esophagus into the stomach with contraction of the muscle fibers of the stomach and esophagus serves as an intrinsic valve mechanism in the absence of a demonstrable anatomic internal sphincter. On the other hand, Lerche[8] was impressed by the double closure mechanism consisting of the constrictor of the cardia and the inferior esophageal sphincter which he demonstrated on cadavers. Kay and Brown[7] had the impression that preservation of the esophagogastric junction prevented gastric reflux and lessened digestive disturbances in patients undergoing partial esophagectomy. Undoubtedly the mechanism of maintenance of cardioesophageal continence is quite complicated and variable.

The role of the inlying nasogastric tube in production of esophagitis and stenosis is not well established. Bartels[2] felt that the tube was not an etiological factor. Of 82 patients with acute ulcerative esophagitis at necrospy, 30 had had gastric intubation but the lesions were no different from those without intubation. Olsen[9] thought that intubation might predispose to esophagitis but doubted that intubation itself was often the cause of serious esophagitis. He did feel that a tube might be harmful in aggravating pre-existing esophagitis. Vinson[11] reported three cases of benign stricture following intubation but there were the additional factors of peptic ulcer and intestinal obstruction. It is possible that increased intragastric pressure from a pressure dressing on the upper abdomen might cause reflux of gastric juice through the esophagogastric junction held partially open by a tube.

DIAGNOSIS

The condition occurs in both sexes and in all age groups. The diagnosis is made by history of dysphagia, roentgen examination with barium, and esophagoscopy. Dysphagia, especially when associated with peptic ulcer, gall bladder disease, or gastric intubation is strongly suggestive of stenosing esophagitis. The dysphagia itself is not different from that caused by other lesions of the esophagus. Roentgen examination with barium localizes and usually defines the extent of the narrowing of the lumen although esophageal spasm associated with esophagitis may produce narrowing out of proportion to the actual anatomic encroachment. The nature of the lesion is further established by esophagoscopy and biopsy. Since the future welfare of the patient is at stake, malignancy should be excluded as the cause of the stenosis. Adequate biopsies usually suffice but occasionally thoracotomy may be necessary. This has recently been impressed on us by experience with two instances of carcinoma at operation in patients who were being treated by experienced endoscopists by dilatation for strictures considered benign on the basis of biopsy. Others have recorded cases of carcinoma developing in benign strictures known to be of long duration.

The majority of benign strictures and stenotic areas are found in the lower half of the esophagus, most of them being in the terminal third. This location is in agreement with the acid-peptic concept of origin since this is the area exposed most frequently to gastric juice in the greatest concentration. Occasionally the segment is long.

The following case is unusual in respect to the length of the segment of esophagus involved. The history is typical but it is interesting to speculate why there was an acute onset when the predisposing factors of vomiting and gall bladder disease had been present for years. Postoperative gastric retention and intubation may well have been the insult necessary to initiate the process.

CASE REPORT

NCBH No. 122883, a 58-year-old housewife, was admitted Jan. 10, 1951, because of dysphagia of ten months' duration. She recalled that ever since childhood she had vomited very easily, especially after eating fatty foods. Since the age of 30 she had had infrequent attacks typical of cholecystitis, some of them being accompanied by mild jaundice. There was no dysphagia. Roentgen ray studies in January, 1950, showed stones in the gall bladder. Diverticula of the colon were noted. The esophagus, stomach, and duodenum were normal with the exception of retained secretions in the stomach after seven hours' fasting. On March 17, 1950, cholecystectomy was done at another hospital. Chronic cholecystitis and cholelithiasis were found. On the second postoperative day a nasogastric tube was inserted and suction applied because of abdominal distension and vomiting. After removal of the tube three days later, she complained of substernal pain on swallowing fruit juices. She was given phenobarbital and belladonna with relief of the discomfort in several days. The insidious onset of dysphagia began shortly after discharge from the hospital. By the middle of May, two months after operation and intubation, she was having great difficulty with solid foods. Dsyphagia progressed slowly, the severity varying from time to time. She subsisted mostly on liquids and lost 22 pounds. In the latter part of July even liquids passed with great difficulty. On August 25, esophagoscopy revealed a smooth constriction 30 cm. from the incisor teeth. Beyond the constriction the esophagus was markedly narrowed and bled profusely on manipulation. Barium studies of the esophagus showed no good primary peristaltic wave. There was a loss of mucosal pattern in the distal two-thirds.

Esophageal dilatation was done several times. Following each dilatation there was very temporary relief of the dysphagia. Biopsy done Oct. 23, 1950, revealed granulation tissue with chronic inflammation. She was referred for further investigation.

On admission ten months after onset of dysphagia there was evidence of moderate weight loss. There was nothing suggestive of collagen disease. Blood volume and blood chemistry examinations were normal. Kahn and Wassermann tests were negative. Skin tests for tuberculosis were negative. Fasting gastric analysis indicated 18 degrees free acid, and 43 degrees total acid. Barium x-ray examination showed marked narrowing of the lumen beginning at a level just below the arch of the aorta extending to the cardia. Peristalsis was absent in the narrowed segment although present above. The esophagoscope encountered marked narrowing 23 cm. from the incisors and could not pass the 30 cm. level.

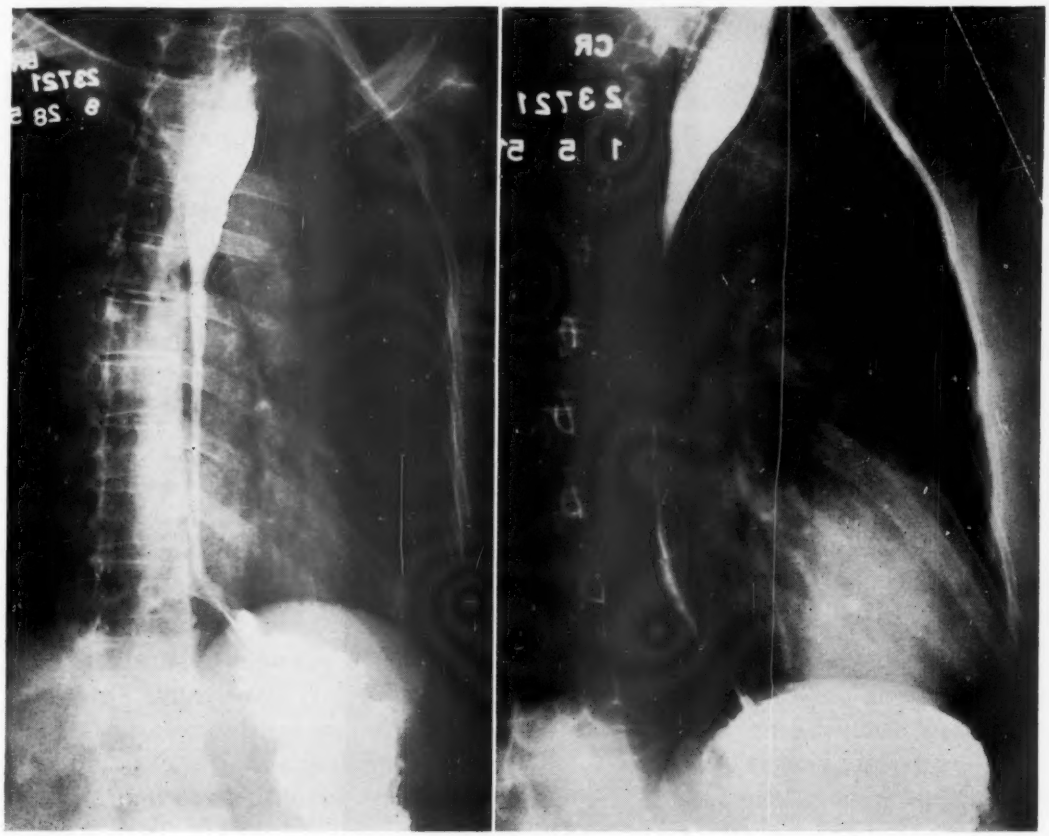

Fig. 1. Fig. 2.

Fig. 1.—Esophagram, Aug. 28, 1950, showing narrowed esophagus.
Fig. 2.—Esophagram, Jan. 5, 1951, showing progression of stenosis.

The mucous membrane of the affected area was dirty gray and bled easily. Biopsy showed acutely and chronically inflamed tissue. Because of the possibility of carcinoma in the depths of the lesion, despite negative biopsies, thoracotomy was done on Jan. 16, 1951. The esophagus was exposed from the hilum of the lung to the diaphragm. The esophageal wall was moderately and diffusely thickened but no area suggestive of neoplasm was found. A long, thin, wedge-shaped piece of tissue including all layers was taken from the longitudinal plane of the esophagus. Microscopic study revealed inflammation without evidence of malignancy. The incisions were closed and gastrostomy was done. She left the hospital on the twelfth postoperative day.

After discharge from the hospital she was allowed nothing by mouth until dilatation was begun six weeks postoperatively. Nutrition was satisfactorily maintained by gastrostomy feeding. Dilatation was begun with the Hurst mercury-filled bougie up to No. 18 French. Then she was able to swallow the bead and thread. Retrograde dilatation with the Tucker dilator was done until a No. 36 French passed with ease. Three months after beginning treatment the gastrostomy stoma was allowed to close and bouginage was continued at less frequent intervals with the Hurst dilator. The esophagus rapidly enlarged to take a No. 50 French easily. She was then able to eat a regular diet without difficulty. Nine months after operation she was able to eat all foods and had regained her normal weight. Bouginage was repeated at infrequent intervals, as much for follow-up as for therapy; the large dilator

Fig. 3.—Esophagram Oct. 25, 1951, nine months after thoracotomy, showing regression of stenosis toward normal. Arrow shows narrowing at the site of biopsy.

passed easily. Repeat esophagram showed great improvement over the previous films. The esophagoscope passed easily the entire esophagus and showed slight residual esophagitis beyond 31 cm. from the incisors.

DISCUSSION

In this case there were several of the usual precursors of esophagitis. Intermittent vomiting had been present for years. Persistent acute vomiting followed cholecystectomy for gall bladder disease. An inlying nasogastric tube had been

used for gastric retention. All of these factors were conducive to admission of gastric juice to the lower esophagus. The esophagus had been normal by x-ray study prior to the first operation. Whether the presence of retained secretions in the stomach on the initial examination was significant is not known.

Treatment is divided roughly into direct and indirect approaches. The direct approach which is anatomic includes dilatation and resection. The indirect approach is physiologic and is based on reduction of acid-peptic irritation. In the present case exposure of the esophagus for examination and biopsy was felt necessary before assuming the lesion to be benign and proceeding with treatment.

The direct approach to treatment which has for its objective the restoration of an adequate pathway includes dilatation, resection, and plastic procedures. A plastic procedure, ideal for short strictures, could not be employed here because of the length of the involved segment. Segmental resection of the esophagus with end-to-end anastomosis was not feasible in this case because of the length of the segment and lack of normal esophagus distally. Esophageal resection with esophagogastrostomy was not done because of the possibility of further stenosis above the anastomosis if reflux persisted. Such an occurrence has been reported.[3] Furthermore, all of the above resective procedures seemed unduly destructive for a lesion which proved reversible after the acute precipitating factors had been removed (postoperative vomiting and intubation).

The indirect approach is physiologic and attempts to reduce the acid-peptic regurgitation. Wangensteen and Leven[12] have reported successful results with subtotal gastric resection in the treatment of stenosing esophagitis. This operation would not have established the benign nature of the lesion in the present instance without the additional procedure of thoracotomy. Subtotal gastrectomy should be reserved for those cases in which there is no reasonable suspicion of malignancy.

The present case was treated with a combination of the indirect and direct methods. Physiologic rest and neutralization of acid-pepsin were accomplished by gastrostomy with frequent feeding. Restoration of an adequate pathway was obtained by dilatation. Thus far the result has been satisfactory. It might appear that the treatment has been unduly prolonged and complicated. Actually the patient resumed her normal activities shortly after discharge from the hospital and the return visits have not been inconvenient.

Although a follow-up of many years will be necessary before such a case can be concluded, response to therapy has been good. With removal of the acute stimuli and the eradication of the chronic gall bladder disease permanent relief is anticipated. Should an exacerbation of significant dysphagia occur, subtotal gastrectomy can then be done.

The problem of acid-peptic action in the esophagus is no less complicated than the duodenal ulcer problem. Certainly not every patient with regurgitation of gastric juice gets significant esophagitis. What additional common denominators are necessary can be learned only from further investigation.

SUMMARY

Production of stenosing esophagitis by reflux of gastric juice is discussed. Methods of treatment are considered. Predisposing factors are enumerated and illustrated in a typical case treated by dilatation and neutralization. Importance of adequate biopsy is stressed.

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A STUDY OF INTESTINAL INTUBATION USING A FLEXIBLE STYLET WITH CONTROLLABLE TIP*

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INTRODUCTION

THE present understanding of the physiologic and pathologic effects of intestinal obstruction was initiated by Hartwell and Houget[17] in 1912. They observed that the lives of dogs with high intestinal obstruction could be prolonged by subcutaneous administration of saline solution. Gamble and Ross[12] discovered the mechanism whereby saline solution serves as a protective agent. The lack of protection in patients with lower intestinal obstruction by saline led to the acceptance of the thesis of absorbed toxic substances from the bowel. The lethal effects of bowel distension in experimental animals and human patients with intestinal obstruction have been clarified by data collected by Wangensteen.[39] Gastrointestinal suction for decompression of the distended bowel was established by Ward[41, 42] Wangensteen[37, 38] and Miller and Abbott.[26, 27, 28] In 1940, McKittrick and Sarris[25] found intubation coupled with better knowledge of electrolyte therapy in patients with intestinal obstruction produced a decline in the mortality rate for the first time in forty years.

Scheltema[30, 31] was among the early workers[7-9, 24, 26, 36] in the field of intestinal intubation. He was the first to transverse the entire intestine of an animal with a long tube. Much later the double lumen balloon-tipped catheter was introduced by Miller and Abbott[26] for use in human patients. The original Miller-Abbott tube was occasionally found to be plugged by gastrointestinal content and often it did not enter the small bowel of the distended patient. Many attempts[1, 3, 6, 10, 15, 16, 18, 20-23, 33, 43, 46] were made to overcome these and other disadvantages through modifications in technique and structure.

Abbott[2] was the first to employ a stylet for insertion of long tubes in patients with intestinal obstruction. The technique was adapted from the original methodology of Rousselot and Bauman. Others[5, 6, 25] have also described its use. The technique applied by these authors consisted of inserting a wire stylet to within 5 or 6 inches of the end of the tube, inflating the stomach with 300 to 500 c.c. of air, placing the tube along the greater curvature of the stomach, then deflating the stomach to propel the stiffened tube into the duodenum. B. A. Smith[33] discarded that method as having too many difficulties and dangers. The apparatus used in this study has been previously described in the literature[35] but the technique of intubation, to be described below, has been modified slightly since the preliminary report.

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*Manufactured by Geo. P. Pilling & Son Co., Philadelphia, Pa.

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TECHNIQUE OF INTUBATION

The stylet, lubricated with petroleum jelly, is introduced through the hole in the side of the tube to a distance of 1 inch from the stainless steel end plug. The patient is placed supine on the fluoroscopy table and the tube, with the stylet in place, is introduced through the mouth into the stomach.

A brief flash of the fluoroscopic screen will reveal the location of the tube. If the tube is pointed to the patient's left (into the fundus), the stylet and tube are retracted into the cardia of the stomach, the stomach is distended with 500 c.c. to 1,000 c.c. of air and the controllable tip is turned toward the patient's right

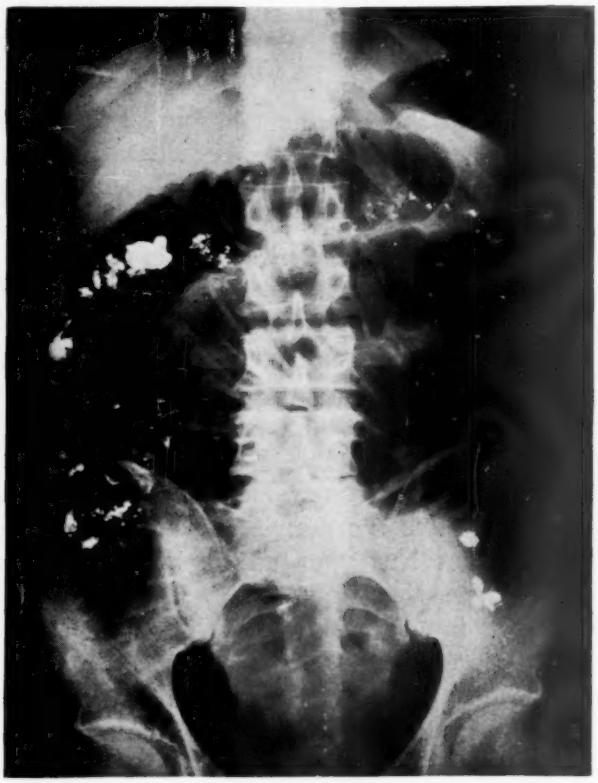

Fig. 1.—Primary small bowel obstruction in a 61-year-old man (M. G.) with incarcerated hernia of 10 days' duration and marked small bowel distention with fluid levels. The residual barium was from a previous large bowel enema prior to admission. There were no signs of strangulation.

side. The stylet and the tube are then advanced along the greater curvature of the stomach until the end of the tube lies in the region of the pylorus. The controllable tip is then manipulated until there is no curve present, rotating the "tension sleeve" of the handle to the right and relieving any tension on the small wires to the tip. Then pressure is exerted on the thumb lever to stiffen the body of the stylet and the tube is advanced into the second or third portion of the duodenum. After the stylet is extracted to 10 to 15 cm., the stylet and the tube are advanced so as to have the tip of the tube in or beyond the third

portion of the duodenum with the controllable tip of the stylet in the second portion of the duodenum. The stylet is again extracted but the tip of tube is not moved. Again the stylet and tube are advanced and the tip of tube is placed in the jejunum and the tip of stylet in the second portion of the duodenum. (This manner of removing the stylet slightly and advancing the tube enables the tube to reach further into the bowel at the initial intubation without the hazard of the stylet making so many turns that it cannot be extracted.) The stylet is then withdrawn from the tubing, the balloon is inflated with 10 c.c. of air, and the hole in the side of the tubing through which the stylet was inserted is closed with a metal insert. All manipulation of the stylet within the intestinal tract is done under fluoroscopy; however, the fluoroscope need be on only for brief periods during the procedure (see Figs. 1 to 6). The tubing

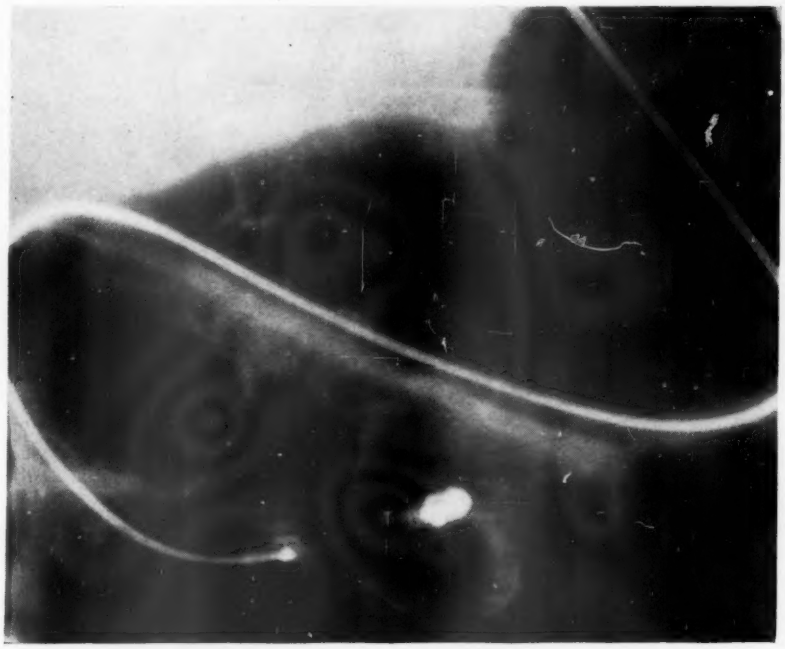

Fig. 2.—The stylet and tube were placed into the stomach, through the pylorus, and into the third portion of the duodenum as described in the text.

should be inserted into the patient's mouth with the natural curvature of the tube and the stylet directed toward the patient's right side. It is placed through the mouth because this route offers the least resistance in extracting the stylet. A catheter may be passed into the nose and out of the mouth; it is then attached to the long intestinal tube and both tubes are extracted through the nasal canal.

Following intubation a supine x-ray film of the abdomen is taken to identify the location of the tube and the size of the balloon bolus. Continuous Wangensteen suction is applied to the large tubing. Nurses are instructed to advance the large and small tubing 8 cm. every hour, at which time the large tubing is irrigated with 30 c.c. of saline solution.

Fig. 3.

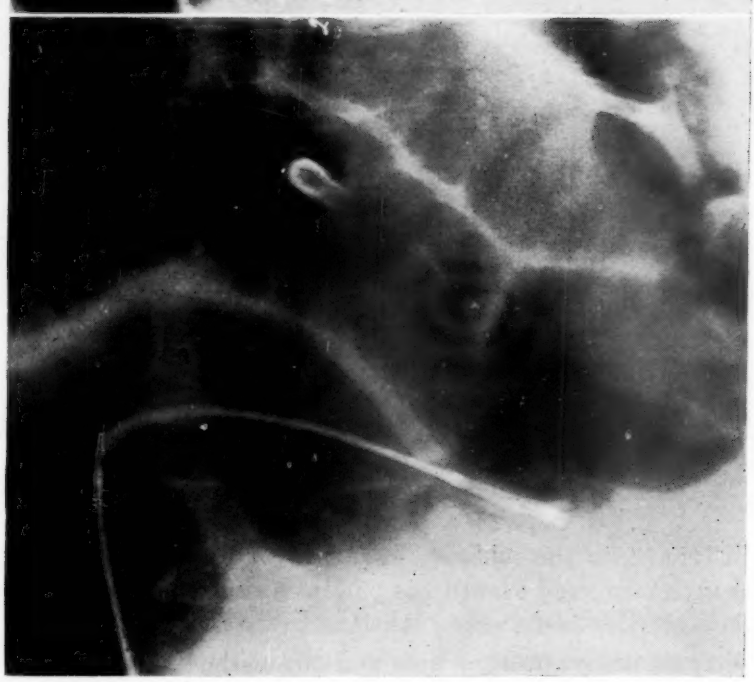

Fig. 4.

Fig. 3.—The stylet was made flexible throughout the body by releasing pressure on the thumb lever. The large loop of the stylet and tube in the stomach was straightened out as much as possible by extracting the stylet and tube without moving the tip of the tube. The stylet was then retracted from the tube until the tip lay in the pylorus as seen above. Note the stainless steel tip of the tube remaining in the third portion of the duodenum.

Fig. 4.—Pressure was placed on the thumb lever of the stylet and the tube and stylet advanced together. Note that the stainless steel tip of the tube had advanced through the ligament of Treitz and into the jejunum. This procedure was repeated and the tube was advanced well into the jejunum (see Fig. 5).

RESULTS

In analyzing the effects of intubation, roentgen examination was of crucial importance and it was by this means that the various gradations of distention were arbitarily defined. Distention of the small bowel is denoted by the presence of gas and fluid in loops of small bowel which measure 4 cm. or greater in diameter on the supine and upright x-ray films. The degree of distention of the colon was diagnosed upon evidence of increased caliber of the bowel and widening of the haustral markings.

Fig. 5.

Fig. 6.

Fig. 5.—Same patient as before (M. G.) showing tip of the tube well into the jejunum 10 minutes after initiating intubation with the stylet technique.

Fig. 6.—Same patient (M. G.) showing excellent decompression of the intestine in 12 hours. This period of time was required for adequate fluid and electrolyte therapy prior to surgery. The above x-ray film was immediately followed by surgical intervention, and strangulation with abscess formation of the distal ileum was found. Following small bowel resection, the patient survived.

The degree of distention of the small bowel was divided into three groups. In the first group, designated slight distention, fell 9.4 per cent of all the cases with clinical evidence of a full abdomen and with radiographic findings of a few loops of bowel. The intestine was distended up to 4 cm. in caliber but there was no definite lengthening of the loops and no marked widening of Kirkring's folds. Twenty per cent of the cases had marked distention, with a tight abdomen and radiographic findings of loops of small bowel over 5 cm. in diameter. In this group of cases, there was lengthening of the loops with fluid levels and wide

separation of Kirkring's folds. A third group, embracing 59 per cent of the cases intubated, had moderate distention showing a tense abdomen clinically, with radiographic findings which fell between slight and marked distention. A final group consisting of 12 per cent of the cases intubated had no distention.

The time of the passage of the tube into the area described in Table I under "location of the tip at initial intubation" is the time from the instant the tube was placed in the patient's mouth until the complete removal of the stylet.

The criteria for successful intubation were those established by Wild.[43] Passage through the pylorus was sometimes difficult to ascertain, but when the tube has reached the lower aspect of the second portion of the duodenum, the initial intubation was considered to be successful. The intubation of a patient with a gastroenterostomy was considered successful when the tube entered 30 cm. into the efferent loop.

A. *Early Results of Intubation.*—Table I includes 180 consecutive trials at intubation. They include 159 cases of intestinal distention and 21 cases without distention. The area reached at the initial trial of intubation in the time stated is correlated with the degree of distention. Cantor[4] describes the ligament of Treitz as the last anatomic barrier to successful intubation. In this study, 64 per cent of the trials at intubation passed into the jejunum. Particularly interesting was the introduction of the long intestinal tube to or beyond the second portion of the duodenum in 92 per cent of the patients with marked distention. There were failures in only 10 per cent of the patients in which intubation was attempted. In one case the tube remained in the stomach and in another it remained in the first portion of the duodenum. These were not considered as failures, for the tip was intentionally left at these levels for diagnostic purposes. Intubation had previously been attempted on each of these patients, employing a different technique, without achieving success.

TABLE I. THE RELATIONSHIP OF THE DEGREE OF DISTENTION AND THE EXTENT OF INITIAL SUCCESS (180 CASES)

LOCATION OF TUBE TIP AT INITIAL INTUBATION	MARKED DISTENTION	MODERATE DISTENTION	SLIGHT DISTENTION	NO DISTENTION	TOTAL NUMBER	TOTAL PER CENT
Jejunum	26	64	13	13	116	64
Ligament of Treitz	3	7	2	3	15	8
Third portion of duodenum	2	15	1	1	19	11
Second portion of duodenum	2	7	1	0	10	6
First portion of duodenum	0	0	0	1	1	0.5
Stomach	0	0	0	1	1	0.5
Failure	3 (8%)	13* (12%)	0	2 (9%)	18	10
Degree of Distention (Total Number)	36 (20%)	106 (59%)	17 (9%)	21 (12%)	180	(100)

*One patient intubated at surgery to third portion of duodenum and the tube could not be advanced further. This is considered a failure.

The average passage time in 162 successful intubations was 11.06 minutes. The passage rates in intestinal distention may be evaluated better by examination of Table II. In those patients with successful intubation, 71 per cent of the

cases were intubated in 10 minutes, while by 30 minutes 97 per cent of the cases were intubated. Attention is invited to the fact that, of the successful intubations of the jejunum, 12 were done at the time of surgery. In this group there were 3 cases with marked distention and 9 cases with moderate distention. In addition, there was 1 failure of passage in a patient with moderate distention at the time of surgery. The average passage rate was 8.4 minutes.

TABLE II. PASSAGE RATES INTO THE SMALL INTESTINE AS RELATED TO THE DEGREE OF DISTENTION

TIME REQUIRED FOR INTUBATION	DEGREE OF DISTENTION				TOTAL	
	MARKED	MODERATE	SLIGHT	NONE	NUMBER	PER CENT
10 min. or less	19	66	15	15	115	71
10 min. to 20 min.	10	16	2	2	30	19
20 min. to 30 min.	3	7		2	12	7
30 min. to 1 hour	1	4			5	3
Totals	33	93	17	19	162	

There were 27 cases with gastric resections prior to the time of intubation. One patient with an abdominal abscess and two with "sleeve resections" of the stomach were failures in attempts to enter the second portion of the duodenum. The remaining 24 were patients with gastroenterostomies who had a trial of intubation of the small bowel; 23 cases (95 per cent) were successful in an average time of 7 minutes. One (5 per cent) nondistended patient with malformation of the gastric stoma was a failure. Wild and Strickler[44] report a failure to pass the gastroenterostomy stoma in 7 of 38 cases or 18.4 per cent.

The advantages of any method which can reduce the time in passing the long intestinal tube is of extreme value. To accomplish this, the intubator must become well acquainted with the entire apparatus before starting to intubate the distended patient. During the early development of this technique, 30 normal patients had trials of intubation before the author employed the method for distended patients. The method is not difficult and several surgical residents mastered the technique after a brief apprenticeship. A comparison of the passage rates with those in other reported series of cases in which a stylet was not used for intubation of the small bowel is revealing. Table III provides such a comparison.

The possibility of perforation of the bowel wall deserves particular consideration. The mechanism whereby the stylet can be made flexible for passage through the esophagus gives added safety to this apparatus. In two instances the stylet made an inadvertent "U-turn" in the esophagus without untoward effect on the patients. The body of the stylet may be made stiff for advancement after reaching the stomach. The distal 10 to 12 cm. of the stylet and tube remain flexible. This feature has enabled me to introduce the stylet and tube through the stoma of several gastroenterostomies of 3 to 5 days' duration. This was done easily and without derangement of the anastomosis. These experiences and the lack of perforation in any of the 180 trials at intubation lead me to feel that this procedure is relatively safe.

TABLE III. A COMPARISON OF THE PASSAGE RATES OF LONG INTESTINAL TUBES USING THREE METHODS OF INTUBATION

TIME REQUIRED	PERCENTAGE OF PASSAGE RATES UP TO AND INCLUDING SPECIFIED HOUR		
	B. SMITH[34] 1,000 CASES	WILD, STRICKLER[44] 248 CASES	G. SMITH 180 CASES
1 hour			90
3 hours	9	58	
12 hours	25	77	
24 hours	47	82	
48 hours	74	85	
Failures	25	15	10

Intubation of the patient at the time of surgery is a definite technical aid in the decompression of distended patients at the operating table. It takes approximately 5 to 10 minutes to insert the tube into the jejunum by this method. The surgeon is then able to place the tube well into the intestine in a short time.[40] This is often used in place of an aseptic decompressive enterotomy.

B. *Therapeutic Effectiveness of Intestinal Intubation.*—The surgeon operating on the obstructed patient without distention is afforded many technical advantages. The distended bowel is the problem that must be met and controlled as early as possible. The control of air and fluid in the afferent loops of obstructed small bowel is best accomplished by intubation and suction. When intubation is not effective for relief of distention and obstruction, surgical intervention becomes a necessary therapeutic endeavor. Often patients with distended bowel can be easily intubated and decompressed at the time of surgery following failure at a trial of intubation at fluoroscopy. The flexible stylet is used in this clinic for introduction of the long tube during anesthesia. If this technique is not feasible, an aseptic decompressive enterotomy is the avenue of aspiration of bowel content.[39] Patients with signs of strangulation of the bowel or marked distention of the colon are surgical emergencies.[40] Marked distention of the cecum due to colonic obstruction is a definite indication for rapid surgical intervention. The various surgical techniques applied in management of the site of obstruction are not described in this paper. The therapeutic and diagnostic usefulness of intubation was evaluated in 142 cases. There were 16 failures to pass the intestinal tube in this group. Thirty-eight of the original group of 180 cases have been excluded from detailed evaluation because of incomplete data. The series were divided into two consecutive groups, consisting of the first 71 and the last 71 attempts at intubation. There were 18 patients without distention among the 142 cases. The patients without distention were segregated into the early (63 cases) and late (61 cases) attempts at intubation. A total of 113 patients (124 attempts at intubation) with intestinal obstruction received critical evaluation of the effectiveness of intestinal suction.

The primary objective of any method of intubation in obstructed patients is the relief of distention. Table IV reflects the ability of this method of intubation to reduce the content of the obstructed bowel. The time required for successful decompression using intestinal suction was determined by clinical and radiographic findings. Decompression was considered adequate by physical examination where the patient's abdomen was soft and flat and/or the x-ray

film of the abdomen indicated loops of bowel less than 4 cm. in caliber. The status of patients treated by intestinal suction was reported as marked, moderate, or slight distention as demonstrated by x-ray films. The number of hours required for decompression was recorded for each of the three degrees of distention and the percentage of patients adequately decompressed during that period of time was tabulated. A total of 97 patients were successfully intubated. Three patients were in terminal condition and died within 6 hours or less without adequate decompression. The remaining 94 patients were successfully decompressed by intestinal suction. During the first 12 hours following initial intubation 20 patients with marked distention (63 per cent), 31 patients with moderate distention (63 per cent) and ten patients with slight distention (77 per cent) were adequately decompressed. In the same groups 75 per cent, 85 per cent and 90 per cent of the distended patients were decompressed within 24 hours.

TABLE IV. THE TIME REQUIRED FOR DECOMPRESSION OF THE BOWEL AS RELATED TO THE DEGREE OF DISTENTION (IN 97 PATIENTS* SUCCESSFULLY DECOMPRESSED BY INTESTINAL SUCTION)

TIME REQUIRED FOR DECOMPRESSION	DEGREE OF DISTENTION					
	MARKED		MODERATE		SLIGHT	
	NO. PATIENTS	PER CENT DECOMP.	NO. PATIENTS	PER CENT DECOMP.	NO. PATIENTS	PER CENT DECOMP.
Up to 4 hours	13	41	13	27	5	38
Up to 12 hours	20	63	31	63	10	77
Up to 24 hours	24	75	41	85	13	100
Up to 48 hours	30	94	44	90		
Up to 48 hours and longer	32	100	49	100		

*Three patients were failures at decompression due to early death (six hours or less). These are not included in this table.

The location of the obstructive mechanism is an important factor in the treatment of intestinal distention. The patients were separated into groups of various types of obstruction, following the classification of Wild and Strickler.[44] They were classified as primary small and large bowel obstruction or adynamic ileus upon admission to the hospital. The patients developing distention following surgery were grouped as mechanical, adynamic ileus, and mixed types of obstruction. The different mechanisms of obstruction and their location present varied problems in decompression. Table V permits a comparison of the results of intubation in the various types of obstruction and indicates the improvement in handling the patients after the method of intubation was well established. The cases were divided into the first 63 and last 61 trials at intubations in patients with distention. Eighty per cent of the first 56 patients intubated had successful decompression. Eighty-eight per cent of the last 57 patients studied were relieved of their distention. The patients with primary small bowel obstruction were adequately decompressed in 75 per cent of the earlier cases and 93 per cent of the later attempts at decompression by intubation. There were 11 failures at intubation in the first group of patients as compared to 5 failures in the last series.

TABLE V. TREATMENT OF DISTENTION

TYPE OF OBSTRUCTION	SUCCESSFUL DECOMPRESSION		FAILURES AT INITIAL INTUBATION
	INTESTINAL SUCTION	OTHER METHODS	
First Series (63 Intubations in 56 Patients)			
Primary small bowel*	19	5	6
Primary large bowel	5		
Postoperative			
Mechanical	12	4	5
Ileus	6		
Mixed	2		
Adynamic*	1		
Total	45	9	11
Last Series (61 Intubations in 57 Patients)			
Primary small bowel*	28	1	2
Primary large bowel		1	
Postoperative			
Mechanical	6	3	3
Ileus	8	1	
Mixed	2		
Adynamic	5	1	
Total	49	7	5

*There were three deaths in six hours or less following initial attempt at intubation. Decompression was unsuccessful in each case.

The time required for decompression of the distended bowel as related to the location and type of obstruction was not included in Tables I to V. The patients were also studied from this point of view. Fifty-seven per cent of 61 patients with primary obstruction of the intestine (primary small bowel and primary large bowel obstruction) were found to have relief of distention in 12 hours. Wild and Strickler[44] reported 43 per cent of 98 patients in this category decompressed in 12 hours. Twelve hours following intubation 48 per cent of 44 patients in this series with postoperative distention of all types were adequately decompressed. Wild and Strickler were able to decompress only 18 per cent of 91 patients with postoperative distention in the same time interval. The six patients with primary large bowel distention were further investigated. Five cases were decompressed in 48 hours or longer and one patient had a transverse colostomy twelve hours after intubation. The long period of time required for decompression by intubation indicates a definite hazard in treating large bowel distention with intubation. The series is small, since in this clinic the majority of patients with large bowel distention are treated by colostomy or with aseptic decompression followed by definitive surgery.

The results of any mode of treatment are the principal concern of the surgeon. This group of patients were studied to determine the effectiveness of this method of intubation. All patients included in Table VI received a trial of intubation therapy. Patients treated by other methods of decompression were all those who had failed to adequately empty the bowel by intubation. The cases with adequate reduction in bowel content were considered as successful decompressions. Several patients with a failure of intubation at fluoroscopy were later intubated and adequately decompressed at the time of surgery; these were considered as successful decompressions by intubation. The patients with successful intubation at fluoroscopy and inadequate reduction of the bowel

content at the time of surgery were included in the group of distentions treated by other means and were judged as failures of this technique. The failures at intubation received operative management. The results of treatment in all 113 cases showed that 54 (48 per cent) were treated with intestinal suction and the obstruction relented without surgical intervention. There were 40 patients (35 per cent) treated with successful decompression with intestinal suction but who required surgery later for relief of the obstructive mechanism. Sixteen patients (14 per cent) were not decompressed by a trial of long intestinal tube suction.

TABLE VI. THERAPEUTIC RESULTS IN INTESTINAL OBSTRUCTIONS (113 PATIENTS)*

TYPE OF DISTENTION	INTESTINAL SUCTION; OBSTRUCTION RELENTED	DECOMPRESSION BY INTESTINAL SUCTION; OBSTRUCTION RELIEVED BY SURGERY	FAILURE OF DECOMPRESSION BY INTESTINAL SUCTION; SURGERY REQUIRED FOR DECOMPRESSION AND RELIEF OF OBSTRUCTION
Primary small bowel	13	34	6
Primary large bowel	1	4	1
Adynamic	6	0	1
Postoperative			
Mechanical	16	2	7
Ileus	14	0	1
Mixed	4	0	0
Total	54 (48%)	40 (35%)	16 (14%)

*Three patients were failures of decompression due to early death (six hours or less). These are not included in this table.

A further evaluation of the 16 failures of decompression shows that there were 11 failures of intubation and 5 successful tube passages that did not evacuate the bowel adequately. (There were a total of 16 failures at the initial trial of intubation. Five of these patients had successful intubation later; one at fluoroscopy and four at the operating table.) The 11 failures of decompression were treated by surgical intervention. Surgery was instituted within 12 hours or less in 4 of the 5 patients with successful intubation and inadequate decompression. The other patient had postoperative ileus and refused further trials at intubation after he had removed the tube himself. Gastric suction was subsequently employed with only partial relief.

There were 3 patients who received inadequate decompression due to early death. Two patients with primary small bowel distention died at 45 minutes and 6 hours, respectively, after a trial at intubation. The former was successfully intubated. The latter was a failure at intubation, his terminal status preventing surgical intervention prior to death. One patient with adynamic ileus died during abdominal exploration and the terminal ileum was found to be perforated. Intubation did not delay surgery in this patient.

MORTALITY STATISTICS

There were 12 deaths (11 per cent) in the 113 patients with intestinal obstruction. Of the patients who died, there were 3 patients seen in terminal condition at the time of intubation who died a short time thereafter. There were 3 patients who died of generalized carcinomatosis with relief of distention.

There were 3 deaths (5 per cent) in the 55 patients treated with only intubation of the small bowel. One of these patients died without decompression within 6 hours after attempts at intubation. The other 2 patients died with successful decompression 20 hours and 8 days, respectively, following intubation. Both of these patients had generalized carcinomatosis.

INTUBATION IN NONDISTENDED PATIENTS

Eighteen patients were intubated for reasons other than distention, with one failure. In this group the intubation was a desirable adjunct in the care of the patient from either a diagnostic or therapeutic point of view. Six patients were intubated to increase their caloric intake by tube feedings. This has been described many times in the past. John Hunter[19] was the first to record this technique of feeding. One patient, who was intubated twice, was given a vermifuge for infestation with tape worms. The tube was placed in the small bowel and the medicinal agent injected through the tube as described by others.[13, 14, 32] Diagnostic aspirations were attempted on 3 patients after the technique of Miller[29] and Abbott.[1, 2] Four patients had small bowel intubation one day prior to repair of a large ventral hernia. This was found to be a definite aid in maintaining bowel decompression postoperatively. One patient with anuria and hyperkaliemia was intubated. It was planned to use intestinal lavage for reducing the potassium blood level. The patient expired 45 minutes after intubation without relief.

There were 16 patients who had a small amount of thin barium introduced into the small bowel through a long intestinal tube for diagnostic purposes. Fourteen of these patients were previously distended and the obstruction had relented prior to this examination. Two patients were not obstructed. The procedure was most helpful in visualization of the bowel anastomoses or small bowel tumors by roentgenographic techniques. The use of intestinal tubes as an adjunct for the diagnosis of intestinal lesions by x-ray examination was suggested by Scheltema[30] in 1908. A recent report of this technique has been written by Friedman and Rigler.[11]

SUMMARY

1. The technique of intestinal intubation with a flexible stylet with controllable tip and its clinical application in 180 trials at intubation are reported.

2. Successful intubation of the small bowel was achieved in 90 per cent of the cases in an average time of 11.08 minutes.

3. One hundred forty-two trials at intubation were evaluated as to their effectiveness as a diagnostic or therapeutic adjunct. There were 38 cases of the original group with insufficient follow-up data.

4. One hundred thirteen patients with intestinal distention and 18 patients without distention were studied as to the effectiveness of this mode of therapy. Eighty-three per cent of the patients with intestinal obstruction were adequately decompressed by intestinal suction.

5. The clinical applications of small bowel intubation in nondistended patients were briefly discussed.

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ARTERIOVENOUS FISTULA OF THE LUNG TREATED BY DISSECTION AND EXCISION WITHOUT PULMONARY EXCISION

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THE purpose of this paper is to present a report of a patient with an arteriovenous fistula of the lung treated successfully by a unique method. The method was that of complete dissection and excision of the arteriovenous aneurysmal sac along with the afferent artery and the efferent vein intact, without sacrifice of any pulmonary tissue. This is the first case treated by this method to our knowledge, although it is recognized that there have been many cases in which this method would not have been applicable because of the location of the fistula deep in the substance of the lung rather than on or near the surface.

Also, the available literature has been reviewed. Because of several features in which we were particularly interested in the case to be recorded here, the previously reported cases have been analyzed in regard to the methods of diagnosis and treatment, the incidence of central nervous system manifestations, and the incidence of multiple pulmonary arteriovenous fistulas. The more usual features of pulmonary arteriovenous fistula have been described in an excellent article by Yater, Finnegan, and Griffin.[39]

There have been 78 cases of arteriovenous fistula of the lung reported through December, 1950. The first case proved and treated by operation was reported by Hepburn and Dauphinee,[23] in 1942. Prior to that time only 7 cases had been reported, 6[6, 9, 14, 29, 30, 37] of which were autopsy diagnoses alone without prior clinical diagnoses. The other was diagnosed clinically and reported by Smith and Horton[34] in 1939, but no surgical treatment was used. It is interesting that since 1942 only 2 cases[1, 38] have been recorded with the diagnosis by autopsy alone. All of the remainder reported since 1942 have been diagnosed by clinical means.

The methods of proof of the diagnosis in the 78 cases were as follows: autopsy or verification by autopsy in 11, clinical in 15, and operation in 52. In 8 of the autopsied cases the clinical diagnosis was not made prior to death, the last of these[38] being reported in 1948, in which case death resulted from a brain abscess.

Of the 78 cases, 51 (65 per cent) have been treated by operation. In the 51 cases, there have been 3 deaths,[2, 10, 36] a mortality rate of 5.9 per cent. Of those operated, 46 cases were treated by unilateral operation and 5 by bilateral operation. The unilateral operations consisted of lobectomy in 26 cases, pneumonectomy in 7 cases, bilobectomy in 7 cases, lingulectomy in 1 case, wedge resection in 1 case, ligation of the pulmonary artery in 1 case, double ligation and division of an aberrant systemic artery in 1 case, and double ligation and division of an aberrant pulmonary artery in 2 cases. In the 5 cases treated

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by bilateral operation, there were 3 wedge excisions of the lung in 1 case, a lobectomy and a contralateral segmental lobectomy in 1 case, 3 lobectomies in 1 case, a lobectomy and wedge excision in 1 case, and a lobectomy and 2 wedge excisions in 1 case. In only 1 of the cases surviving has there been a report of persisting cyanosis.[4]

In the 78 cases reported previously, there have been 25 cases (32 per cent) of multiple fistulas of the lung. In these, the diagnoses were established by clinical means in 3 cases, operation in 12 cases, and autopsy in 10 cases. Some of the cases of multiple fistulas have been unilobar, some unilateral, and some bilateral. Twelve of the 78 cases have been autopsied; in 10 of these, multiple fistulas have been found.

The incidence of symptoms or signs referable to the central nervous system in cases of pulmonary arteriovenous fistula is of great interest. Such manifestations have occurred in 21 (27 per cent) of the 78 previously reported cases. Convulsions have been the most frequent manifestation, occurring in 10 of the 21 cases. Hemiplegia has occurred in 5 of the 21 cases; in 1 case it was bilateral. The hemiplegia in all cases was transient. Other central nervous system manifestations have occurred in 12 of the 21 cases. These have included transient unconsciousness, localized weakness, paresthesia, syncope, thick speech, numbness, and visual and auditory disturbance in combination with strabismus. The explanation for the appearance of the central nervous system manifestations is not at all clear. Autopsy was performed in 8 of the 21 cases. In 4 of the 8 cases, examination of the brain was not permitted in 1 case, and the findings in the brain were not mentioned in 3 cases. In the other 4 cases, the brain showed only edema in 1, and a cyst without evidence of arteriovenous fistula or hemangioma in another. Brain abscess was found in the other 2; in 1 of the 2, there was no arteriovenous fistula present in the brain; in the other the presence or absence of arteriovenous fistula of the brain was not mentioned.

Convulsions occurred in 3 of the 8 cases that were autopsied. In 1 of the 3 cases, examination of the brain was not permitted. In another, the brain findings were not mentioned. In the third there was a brain abscess but the presence or absence of arteriovenous fistula of the brain was not mentioned.

Hemiplegia occurred in 1 of the 8 cases autopsied and in this case there was found a brain abscess without any evidence of arteriovenous fistula.

Other manifestations of central nervous system involvement occurred in 4 of the 8 cases autopsied. In 2 of the 4 cases the brain findings were not mentioned. In 1, the brain was normal except for the presence of edema. In the remaining case there was a cyst present in the brain but there was no evidence of hemangioma or arteriovenous fistula.

In this regard, it should be noted that in two series of cases of vascular lesions of the brain including arteriovenous fistula reported recently, none of the cases had an associated pulmonary arteriovenous fistula.[28, 35]

CASE REPORT

L. W. (Roper Hospital No. 5357), a 33-year-old Negro woman, was admitted on Aug. 21, 1949. Her chief complaint was substernal pain of two days' duration. The pain was sudden

in onset, radiated to the back, and was associated with generalized weakness. She thought she might have had fever for the previous week, with chilly sensations and sweats each evening. There were no other symptoms. After it was noted on physical examination that the lips and nail beds were cyanotic, she stated on questioning that her nails had been "blue" ever since she could remember. She had never had dyspnea and had done hard physical work in the fields as the wife of a farmer. She was always able to work as hard and as long as anyone else.

Past History.—She was in the hospital in 1942 because of vaginal bleeding. There was a history of frequent spontaneous epistaxes. At that time she was found to be 7 months pregnant. The heart and lungs were normal. Blood pressure was 114/84. The day after admission she delivered a stillborn infant. For the next two weeks she had fever of unexplained origin. In addition, on the fifth day post partum she noticed a speech difficulty and was found to have left hemiparesis. Blood Wassermann and Kline tests were negative.

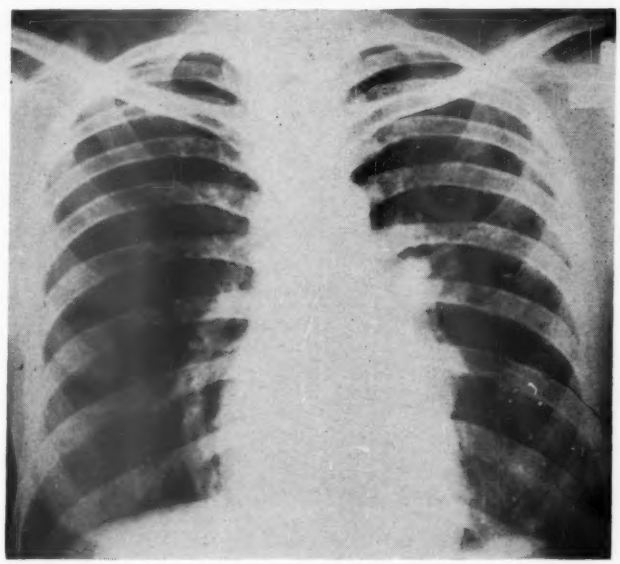


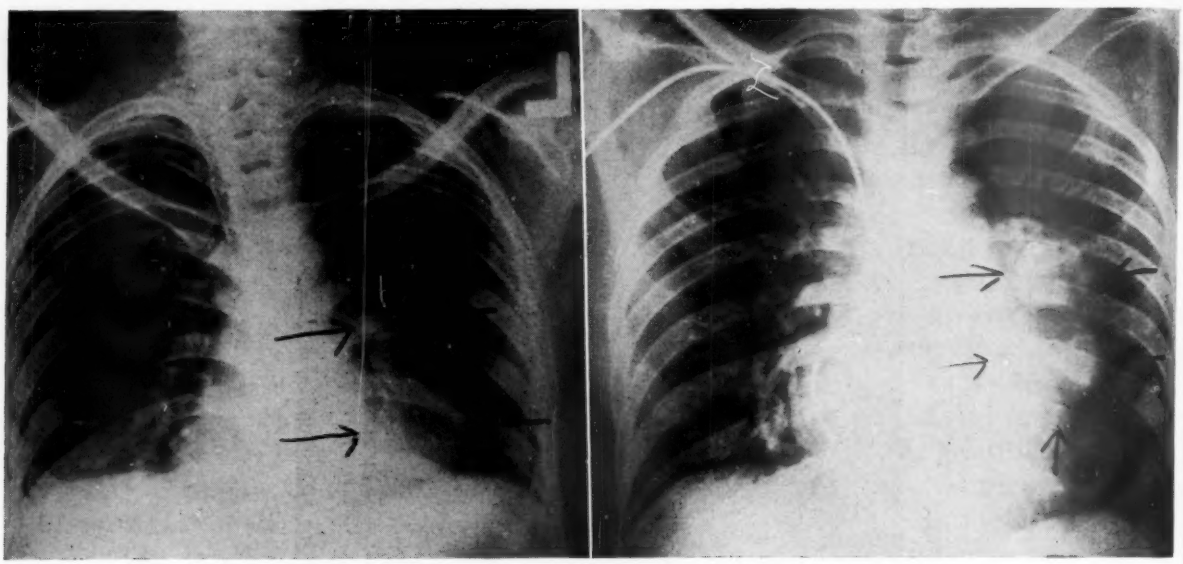
Fig. 1.—X-ray film of chest showing the large bilobular shadow of a mass in the left hilum.

On lumbar puncture, the spinal fluid cell count and total proteins were normal, and the Wassermann, Kline, and colloidal gold tests negative. The routine blood studies revealed severe anemia. Various studies indicated no evidence of blood dyscrasia. There were no notes concerning the presence or absence of cyanosis. An x-ray film of the chest was not made. On discharge from the hospital she was improving markedly and spontaneously.

She was not seen again until October, 1948, when she visited the clinic with a history of fainting spells. No conclusions were reached. Later it was learned that also in October, 1948, she had an x-ray of the chest made in a mass survey and there was found an abnormal shadow in the left hilum (Fig. 1). The patient did not report for further examination at that time as instructed.

Physical Examination.—The weight was 130 pounds, temperature 100° F., pulse 100, respirations 50, blood pressure 100/82. The patient was well nourished and well developed, in acute distress, unable to lie down because of severe substernal pain. The pupils were normal. There were two small petechiae in both conjunctivae. Optic fundi were normal. There was an inconstant systolic murmur along the left cardiac border in the second and third intercostal spaces. Otherwise, the heart and lungs were normal. There was distinct cyanosis of the lips and nail beds and slight clubbing of the fingers. The remainder of the examination was normal.

Accessory Examinations.—Red blood count was 4,350,000, hemoglobin 12 Gm., white blood count 12,600, differential normal. Later examinations revealed no significant change. Urinalysis showed a specific gravity of 1.022, albumin 1 plus; microscopically, occasional red blood cells were seen. Later urinalyses were normal. Blood Wassermann and Kline tests were positive on two examinations. Bleeding time was 1 minute 25 seconds, clotting time 3 minutes, 10 seconds, platelet count 240,000. Fasting blood sugar was 95 mg. per cent, blood urea nitrogen 12 mg. per cent, serum calcium 9.6 mg. per cent, vital capacity 2,400 c.c. Circulation time, arm to tongue, was 19 seconds. This was repeated and found to be 20 seconds. Six blood cultures before Aug. 26, 1949, showed no growth. Blood culture on August 26 was positive for nonhemolytic *Staphylococcus aureus.* Thereafter six blood cultures were negative until Sept. 3, 1949, when another was positive for nonhemolytic *Staphylococcus aureus.* Thereafter four blood cultures were negative. Tests for sickling of red blood cells



A. *B.*

Fig. 2.—X-ray films of chest (*A*) before and (*B*) during the injection of a radiopaque dye into the right side of the heart via an intravenous catheter, demonstrating the increased opacification of the shadow in the left hilum.

were negative. Spinal fluid showed normal cell count and total proteins, negative Wassermann, Kline, and colloidal gold tests. Tuberculin test was negative. Culture of the sputum was negative for acid-fast bacilli. Electrocardiograms preoperatively and postoperatively were normal. X-rays of the entire gastrointestinal tract, using barium as a contrast medium, were normal. X-rays of the skull were normal. Postoperatively an electroencephalogram revealed a mild generalized dysrhythmia with a possible focus in the right temporoparietal area. X-rays of the chest on admission revealed a large bilocular shadow in the left hilum (Fig. 2). Studies of the oxygen content of the arterial and venous blood before and after operation were made, but the results were too inconsistent on several occasions to be considered reliable.

Preoperative Course.—Following admission, the substernal pain subsided promptly and thereafter she had no symptoms although there developed petechiae in the nail bed of the right great toe and in the buccal mucosa. Cardiac catheterization was performed for the purpose of making pulmonary arteriograms and the x-ray films showed a marked increase in density of the left hilar shadow indicating that it was vascular in origin (Fig. 2). Gastroscopic and sigmoidoscopic examinations were performed because of the possibility of multiple telangiectases but none were found.

In view of the increased opacification of the left hilar shadow during pulmonary arteriography, it was believed that the lesion of the left lung was an arteriovenous fistula. The etiology of the fistula was unknown. She had no fever at any time for the four weeks prior

to operation even though two of the blood cultures were positive. She received no sulfonamide or antibiotic therapy.

Operation.—On Sept. 16, 1949, under endotracheal anesthesia, a left posterolateral thoractomy was performed through the sixth intercostal space. The pleural cavity was normal and the lung was allowed to collapse. Protruding from the anterior segment of the upper lobe at its free margin, there was a cystlike mass, 5 by 4 by 4 cm., which appeared not unlike a gall bladder in size and shape. The tip of the mass was adherent to the pericardial fat at the apex of the heart and was dissected from it. The wall of the cystic mass

Fig. 3.—Operative specimen consisting of arteriovenous aneurysmal sac along with the afferent artery and efferent vein.

generally was 1 or 2 mm. in thickness and opaque except for one small area where it was very thin and transparent. Through the transparent area blood could be seen coursing rapidly through the mass and at frequent intervals alternating columns of light and dark blood swirling within. There was a slight thrill over the mass. The pulmonary artery was dissected and occluded by traction on an encircling ligature following which the thrill in the mass disappeared and the color of the patient improved immediately. The two main tributaries of the superior pulmonary vein were likewise occluded. These tributaries appeared to be a small one consisting of the lingular vein and a very large one which appeared to be the trunk of the confluence of the apical-posterior and the anterior segmental veins. The inferior pulmonary vein was then likewise occluded by traction on an encircling ligature. After obtaining full control of the blood supply of the lung, the sac was opened. With a finger inserted in it, it was dissected from the lung where the cystic mass extended into its substance. The mass extended into the substance of the lung for a distance of 4 or 5 cm. and appeared to terminate roughly in the region of some dilated vessels projecting above the surface of the lung over an area of 1 cm., about 4 cm. away from the free edge of the anterior segment. The sac was dissected with relative ease until its base was reached. At this point a large

vessel opening could be seen in its base and a probe inserted into it, showed it to be a dilated vein leading from the sac. This vein appeared to be the mian anterior segmental vein. By incising the overlying visceral pleura and working in the intersegmental plane this vein was dissected easily. After ligation of several small tributaries on the hilar side of the aneurysmal sac, the anterior segmental vein was doubly ligated and divided just short of its confluence with the apical-posterior vein. Later it was completely excised along with the aneurysmal sac. Also at the base of the aneurysmal sac, there were multiple smaller openings of vessels, at least five or six in number, through which blood entered the sac on release of the constricting ligature about the pulmonary artery. Probes were inserted into several of these arterial orifices and they all appeared to be derived from the anterior segmental artery. This was dissected toward the hilum with minimal trauma to the lung tissue and several very small branches of it were ligated. The artery was doubly ligated and divided just distal to its emergence from beneath the apical-posterior vein and it, too, was completely excised along with the aneurysmal sac. Thus the arteriovenous aneurysmal sac was excised in toto along with the afferent artery and the efferent vein, without sacrifice of pulmonary tissue (Fig. 3). In dissecting the anterior segmental artery, a small bronchus was divided when mistaken for the artery. The distal end was ligated and the proximal end was closed with terminal silk sutures. Upon completion of the above procedure, there was a V-shaped defect in the anterior segment which was obliterated with interrupted silk sutures in the visceral pleura. After complete excision of the aneurysmal sac along with the afferent artery and the efferent vein, no thrill could be felt in any of the pulmonary vessels and no evidence could be found of any other vascular abnormality. After complete expansion of the left lung, the wound was closed in layers with interrupted silk sutures throughout after inserting intercostal catheters in the second intercostal space anteriorly and in the eighth intercostal space in the posterior axillary line for closed drainage of the pleural cavity postoperatively. Prior to closure, 100,000 units of penicillin contained in 50 c.c. of normal saline solution were instilled into the left pleural cavity. Upon completion of the operation the patient's condition was entirely satisfactory, but there was still a slight degree of cyanosis evident in the nail beds.

Pathologic Report.—The specimen (Fig. 3) consisted of an ovoid saccular structure measuring 3.5 by 1.5 by 2 cm. There were two stringy portions of tissue, resembling blood vessels, attached to it. Microscopic sections of the aneurysmal wall, apparently chiefly venous in origin, showed fibrous, thickening subintimal tissues with organizing thrombotic materials attached to the lining. There were remnants of lung tissue about the periphery of the aneurysmal sac.

Postoperative Course.—The patient's recovery was prompt and satisfactory. She received a total of 5,100,000 units of penicillin. The murmur along the left sternal border disappeared. Postoperative x-ray films of the chest revealed a shadow considered to be a hematoma in the space from which the sac was removed. This shadow disappeared slowly in subsequent weeks. The nail bads were normal in color at times, but generally they exhibited a slight duskiness. She had a convulsion involving mainly the left face and arm shortly before her discharge, and Dilantin Sodium therapy was begun. On discharge, she was asymptomatic. Since discharge, she has been observed in the clinic at regular intervals. Similar convulsions have occurred on several occasions at long intervals, during periods when she failed to take Dilantin Sodium. Otherwise, she has had no complaints, and has resumed her usual occupation. The slight cyanosis of the nail beds has persisted. The blood pressure and routine blood counts have remained within normal limits. On one readmission to the hospital, pulmonary arteriograms with the tip of a catheter in the left pulmonary artery were made. Most of the dye entered the left lung and revealed an entirely normal vascular pattern. On another readmission, intracranial arteriograms were made, and the vascular pattern was normal. The presence of another pulmonary arteriovenous fistula in the right lung is suspected, and it is planned to make further pulmonary arteriograms in the near future.

DISCUSSION

The recognition of arteriovenous fistula of the lung has occurred with increasing frequency in recent years. This has been the result of the markedly

increased interest in the surgical treatment of intrathoracic diseases, and of a concomitant development of new techniques for accurate diagnosis, especially angiocardiography.

The etiology is unknown. By nearly all observers, it is considered to be a congenital defect. It is associated at times with telangiectasis in other parts of the body. There is evidence to support a strong hereditary factor in its incidence.[27]

The clinical features in the case reported here were the usual ones, except for the absence of polycythemia. The occurrence of the convulsions is inexplicable at present. It has been suggested that the cause might be cerebral embolism due to the entrance of air into the pulmonary vessels at the time of hemoptysis.[11] However, hemoptysis was never experienced by our patient. We can only surmise, in view of the autopsy studies, that the cause might be some physicochemical change in the blood in the presence of a decreased oxyhemoglobin saturation.

The persistence of cyanosis following operation, in the absence of any other definite cause, almost certainly indicates that another arteriovenous fistula of the lung is present which has not been discovered. It has been recorded by some authors that there have been more pulmonary arteriovenous fistulas on gross examination of the lungs at autopsy than were demonstrable during life. Therefore, it is believed that persistent search will result in proof of the presence of one or more additional fistulas, probably in the right lung.

SUMMARY

A patient with a pulmonary arteriovenous fistula is reported.

The technique of successful excision of the aneurysmal sac which was the site of the fistula, along with the afferent artery and the efferent vein, without sacrifice of pulmonary tissue, is described.

Pertinent data from a review of the literature on patients with arteriovenous fistula of the lung are presented with regard to the methods of diagnosis and treatment, the incidence of central nervous system manifestations, and the incidence of multiple pulmonary arteriovenous fistulas.

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THE EFFECT OF PREGNANCY ON THE TENSILE STRENGTH OF HEALING LAPAROTOMY WOUNDS IN RATS

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ALTHOUGH numerous pregnant women have undergone laparotomy for various lesions with uncomplicated healing of the incisions, there have been no reports of controlled tensile strength studies of healing wounds in pregnancy. Such a study is of some interest to the surgeon who may be called upon to perform an operation on a pregnant woman. Of more fundamental significance, however, is the relationship of the healing process to the complex endocrine mechanisms of pregnancy.

One of the adrenal cortical steroids, cortisone, has been shown to inhibit fibroplasia and granulation in surface wounds, as well as to reduce the tensile strength of healing wounds in rats.[1] Adrenocorticotropic hormone (ACTH) likewise affects the healing process, but not to as great a degree as cortisone.[2] The dosages of cortisone and ACTH used in these studies were rather large. Maximal inhibition of healing in rats did not occur until 40 mg. of cortisone per kilogram of body weight were given.

It is known that pregnancy produces an outpouring of adrenal cortical hormones.[3] It is this secretion which may explain the relief from rheumatoid arthritis which occurs in pregnancy. It was considered by the authors that pregnancy would provide a good stimulus for the endogenous secretion of adrenal cortical hormones in dosages which would then necessarily be within the physiologic range, thus eliminating the question as to whether the hormone dosage employed is beyond the capability of the adrenal glands to secrete in vivo.

MATERIALS AND METHODS

Pregnant rats, weighing approximately 200 Gm., were obtained from Rockland Farms, as were the nonpregnant female rats used for controls. All rats were from 14 to 20 weeks old at the conclusion of the experiment. They were maintained in individual cages on an ad libitum intake of Purina Laboratory Chow prior to, and following the laparotomy incision. All animals appeared to be in excellent nutritional condition and their weight curves were satisfactory prior to and during the experiment. Four animals showed weight losses due to intercurrent infections and were discarded without testing the wounds. The actual food intake was not measured. Under ether anesthesia, a standard 3 cm. right rectus laparotomy incision was made, using aseptic technique. It was repaired by means of six interrupted fine stainless steel wire sutures to the peritoneum and to the anterior rectus sheath. The skin was closed with a continuous wire suture. On the third, fourth, fifth, and sixth postoperative days, respectively, the bursting strength of the laparotomy wound was tested by

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inflating the peritoneal cavity with air under pressure according to a previously described technique.[4] The pressure of air necessary to produce bursting of the wound was recorded in millimeters of mercury.

After testing the wound, each animal was killed and autopsy was performed to confirm the existence of the pregnant state. A few animals delivered a day or two prior to the determination of wound bursting pressure. These animals showed results which were not significantly different from those obtained in animals which did not deliver. Those rats which were thought to be pregnant at the start of the experiment, but which later proved not to be so, were then included with the results of the control series.

RESULTS

The results are listed in Table I and Fig. 1. On each postoperative day

TABLE I. BURSTING PRESSURE OF LAPAROTOMY WOUNDS IN PREGNANT AND NONPREGNANT RATS

DAYS PO	SERIES	NO. OF ANIMALS	MEAN BURSTING PRESSURE MM. HG	TEST OF STATISTICAL SIGNIFICANCE*		
				STANDARD DEVIATION	T	P
3	Normal	10	37.6	9.1	3.62	less than .01
	Pregnant	5	28.2	3.1		
4	Normal	11	49.8	5.6	2.75	.012
	Pregnant	13	38.8	11.6		
5	Normal	10	61.0	6.6	6.76	less than .01
	Pregnant	8	36.0	8.2		
6	Normal	10	84.0	7.1	6.04	less than .01
	Pregnant	9	50.9	14.6		

*The t-test as described by Fisher.[5]

tested, the pregnant rats showed a lower bursting pressure than did the control animals. The results were submitted to the t-test of statistical significance according to Fisher,[5] and the differences proved to be significant on each day tested.

DISCUSSION

The period of gestation for albino rats is about three weeks. It is usually not feasible to detect pregnancy by abdominal palpation until the tenth day of gestation. For this reason the rats employed in this study of wound healing were in the latter stages of gestation, probably the equivalent of the third trimester in humans. Although our clinical experience with the healing of laparotomy wounds in pregnant women has been good, these results nevertheless demonstrate that in the latter phases of pregnancy in the rat, there is a definite retardation of wound healing.

In considering the possible pathogenesis of this inhibition of healing, two factors must be considered. First, there is the possibility that the endogenous secretion of adrenal corticoids was stimulated by the pregnancy to such an extent that it resulted in the inhibition of healing. In view of the large dosages of cortisone which must be administered before experimental wound healing is retarded[2] it would seem that this mechanism is unlikely. However, it may be

that the complex combination of endocrine secretions which are produced during pregnancy may have the effect of directing metabolic raw materials to a site which has a higher priority requirement, namely the pregnant uterus.

Another consideration, the importance of which is difficult to assess, is the increased mechanical strain placed upon the healing laparotomy wound by the presence of a greatly enlarged pregnant uterus. It would be possible to eliminate this factor by studying the effect of pregnancy upon the healing of

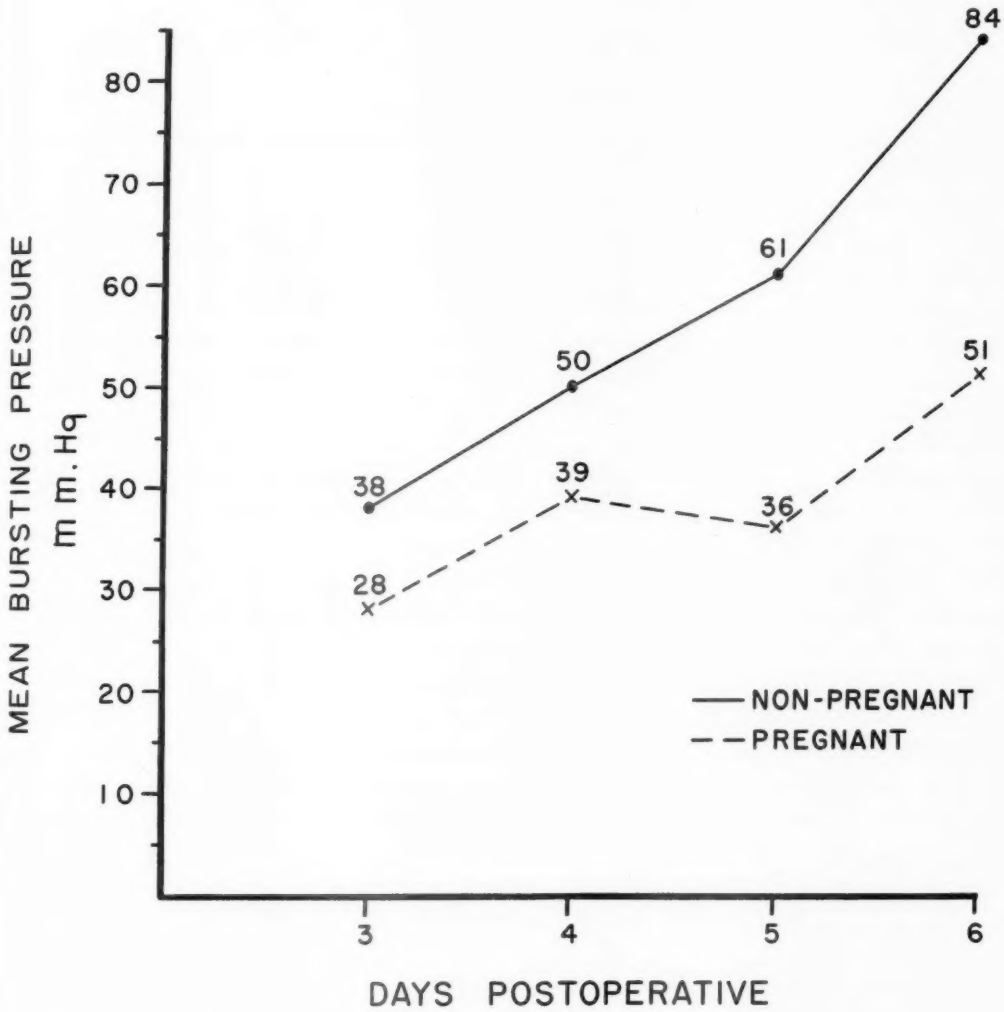

Fig. 1.—Curve of wound healing in pregnant and non-pregnant rats.

wounds made in the skin of the back, which is relatively unaffected mechanically by the increasing girth of the pregnant animal. Unfortunately, the healing of a surface skin defect is slow as compared with the brief period of gestation in the rat, so that the pregnancy would in most cases be terminated long before the wound had an opportunity to heal completely. Tensile strength studies of the healing linear incision in the skin might at first glance appear to provide

a good approach to this problem, but in our experience, studies of this type are relatively inaccurate. This is perhaps due to the difficulty in preventing varying degrees of bacterial contamination from reaching a superficial skin wound following the operation. Nevertheless, studies of this type will probably be necessary in order properly to be able to evaluate the relative importance of the mechanical and the endocrine factors.

SUMMARY

1. Pregnant rats showed a marked diminution in tensile strength of healing laparotomy wounds as compared with normal, nonpregnant female rats.

2. The possible factors in the pathogenesis of this condition are discussed.

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ACUTE PROGRESSIVE UNRELENTING RENAL FAILURE

A Manifestation of Severe Shock Associated with Upper and Lower Nephron Nephrosis

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THERE are increasing indications that the acute renal insufficiency due primarily to tubular damage, which Lucké designated as lower nephron nephrosis,[1] can be divided into several clinical types. The most common clinical type is recoverable, particularly when a conservative regime of management is stringently followed.[2, 3] This type, as a rule, has three clinical phases,[4, 5] namely, the phase of shock, which appears to be its most common antecedent and/or aggravating cause; the phase of maximal renal failure, which may last for eight to fourteen or more days; and the phase of recovery, which is heralded by diuresis lasting for seven to ten days and is followed by a period of renal convalescence. This period is usually of minor consequence to the patient and lasts 1 to 6 months during which renal function returns to its former status. Three variants within this common recoverable type are apparent at present. First, the degree of recoverable renal failure may vary markedly. Thus, it is possible to classify such cases into mild, moderate, and severe forms. Arbitrary clinical criteria may be utilized for this separation. A mild case enters into the phase of diuresis within 5 days, and accordingly, has a mild azotemia, minimal or no acidosis and hypochloremia, and frequently a rapid return of the concentrating power of the kidneys. A moderately severe case enters into the diuresis within 5 to 10 days and displays a fairly pronounced level of azotemia, definite but variable acidosis and hypochloremia and a prolonged interval of isosthenuria. The severe case remains oliguric (urine volume less than 1,000 c.c. with low specific gravity) for 10 days or longer and displays a prominent acidosis, hypochloremia, and a prolonged renal convalescence. Hyperkaliemia is, at times, an added complication of this variant. The severe case, when recoverable, although not displaying diuresis within 10 days, ordinarily reveals signs of renal recovery by this time, mainly in the form of a progressively increasing urine flow. The diuresis is usually entered into within 12 to 14 days.[6] Recently, we have observed a most severe form of acute renal failure with recovery. A patient had a prolonged interval of shock following the intake of 500 c.c. of incompatible blood (Type A given to Type O) and remained oliguric for 3 weeks, entering into the phase of diuresis after 21 days. This patient, treated conservatively throughout, represents one of the most severe variants of this form of renal failure.

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Second, another variant of the recoverable type has been recently discussed.[7] In this form, the patient has a moderate or severe form of renal failure which during and following the phase of diuresis displays a prominent degree of renal salt (NaCl) wastage. The period of salt wastage has been observed to extend for as long as 40 to 60 days, during which time as much as 300 to 800 meq. (18 to 48 Gm.) of sodium chloride daily may be required in order to maintain balance. Following this interval the kidneys recover their ability to conserve salt. One must be vigilant for this potential complication for otherwise severe grades of the syndrome of salt deficit may ensue. Moreover, the recoverable nature of this complication has indicated the need for the prolonged high salt intake.

Third, during the progress of what appears to be by all indications a moderate or severe form of recoverable renal insufficiency there may develop outstanding extrarenal and extrauremic complications which of themselves or in combination with the uremia may prove fatal. It does not appear just to consider such deaths as entirely uremic. Several complications, which have been encountered, include: massive pulmonary embolism, an existing pulmonary carcinomatosis with dyspnea and cyanosis, an existing diffuse pneumonitis with cyanosis, anasarca with pulmonary edema and bronchopneumonia, and the so-called water intoxication syndrome.

In the present communication we wish to discuss still another type of acute renal insufficiency due to tubular damage (acute tubular nephropathy) which appears to be distinct and apart from the above variants both by its clinical manifestations and the morphologic changes observed in the kidneys by post-mortem examination. One such case has been reported from this institution.[8] In the present report the collective characteristics of 10 such cases together with the post-mortem examination of 8 cases are presented. In addition, the prognostic and therapeutic outlook for this type of renal insufficiency will be discussed.

This latter type has been characterized clinically by an acute, progressive, unrelenting renal failure which, so far, in our experience, has yielded to none of the therapeutic approaches attempted. It has been closely related to a prolonged period of profound shock. Morphologically, its outstanding feature has been the demonstration of advanced damage to the proximal and distal segments of the renal tubules (universal tubular damage or upper and lower nephron nephrosis).

CLINICAL FEATURES

The main clinical features of the 10 patients displaying acute progressive unrelenting renal failure due to upper and lower nephron nephrosis, which appear to identify this type, will be discussed. All of these patients were managed by a conservative regime for all or part of their course. Four patients had peritoneal irrigation subsequently.

1. *Sex and Age.*—The group consisted of 6 male and 4 female patients. The ages varied from 9 to 60 years (9, 21, 24, 30, 32, 37, 43, 45, 49, 60). Thus there was no indication of the significance of either age or sex.

2. *Cause of the Renal Failure.*—The renal failure in these cases became apparent in the wake of a prolonged interval of peripheral circulatory failure. The latter was evident by the usual clinical signs, the outstanding of which were hypotension and tachycardia. The clinical evidences of shock were apparent during intervals varying between 6 and 48 hours. Where shock was prolonged it was periodically ameliorated by means of blood transfusions and other infusions. Eight patients experienced blood loss, either as a result of trauma or major operative procedures; 4 of these in addition received at least 500 c.c. of incompatible blood which further aggravated the blood loss.[2] An additional patient exhibited a fulminant hemolytic anemia accompanied by hemoglobinemia and hemoglobinuria. One patient, a psychiatric case, had a marked water and salt deficit and profound shock.

3. *Duration of Renal Failure Prior to Death.*—All of these patients succumbed with renal failure. The duration of the renal failure before death varied between 9 and 22 days (9, 9, 9, 14, 15, 16, 16, 16, 17, 22).

4. *Uremia.*—Table I depicts a summary of various features of the uremia.

TABLE I

DAYS	BLOOD UREA (IN MG./100 C.C.)	PLASMA CHLORIDE (IN MEQ./L.)	PLASMA HCO_3 (IN MEQ./L.)	DAILY URINE VOLUME (IN C.C.)	MEAN BP (IN MM. HG)	RESPIRATORY RATE PER MINUTE	HEMOGLOBIN (IN GM./100 C.C.)
2 and 3	179	95	26	179	93	23	11.5
	(75-330)	(84-102)	(20-30)	(30-625)	(80-112)	(20-32)	(9.5-15)
4 and 5	253	90	24	116	118	25	9.7
	(172-342)	(84-100)	(20-28)	(50-225)	(99-130)	(18-40)	(7-11)
7 and 8	422	85	19.5	140	120	25	8.9
	(292-488)	(72-101)	(12-27)	(50-300)	(98-140)	(20-36)	(7-10)
9 and 10	422	86	22	244	117	33	9.7
	(250-488)	(67-103)	(15-31)	(75-600)	(87-147)	(24-64)	(5.6-13.5)
11 and 12	369	90	20	262	122	32	8.8
	(236-472)	(82-99)	(12-27)	(76-500)	(90-150)	(24-44)	(6.2-12.3)
13 to 16	345	98	19	440	123	33	9.9
	(280-387)	(87-107)	(13-27)	(47-1000)	(82-143)	(28-40)	(9-10.7)

The data depict the mean values and ranges for the various determinations on the ten patients. The highest values for the days chosen were selected. The mean blood pressure was taken as the diastolic pressure plus one-third of the pulse pressure.[13] At least seven values were averaged except for days 13 to 16 when as little as four values were all that were available. The hemoglobin from the patient with hemolytic anemia was deleted.

a. Azotemia soared rapidly reaching a maximum in approximately 7 days, thereafter remaining fairly steady, except in the cases where peritoneal irrigation was instituted. Although the level of azotemia was comparable to that of a severe grade of recoverable acute renal insufficiency during the first week, it naturally tended to remain high longer when extrarenal measures were not interposed, and beyond 7 days reached the highest levels we have observed in the human being. Thus, the over-all retention of waste products tended to be greater than that observed in the spontaneously recoverable types.

b. Hypochloremia was a common finding. Only 1 case, previously recorded,[8] failed to reveal this abnormality. In Table I it will be noted that the recession of plasma chloride concentration, as revealed by the mean values of all cases,

reached a low of 83 meq. per liter by the end of the first week. Five patients who developed an uncontrollable diarrhea revealed a plasma chloride concentration below 80 meq. per liter.

c. Acidosis became a prominent feature. As depicted in Table I the acidosis became pronounced toward the end of the first week. At this time, or shortly thereafter, 8 patients revealed a plasma bicarbonate concentration of 20 meq. per liter or less. Severe acidosis (11 to 14 meq. per liter) was noted in 4 patients. The acidosis was difficult to combat.

d. Serum potassium determinations were performed on 4 patients; 1 showed hyperkaliemia. Although the study of this ion left much to be desired, prior to the terminal period there were no apparent clinical or electrocardiographic evidences of hyperkaliemia. However, the threat of hyperkaliemia was minimized by the use of peritoneal irrigation in 4 patients.

e. The persistent and pronounced oliguria coupled with the sustained azotemia were the main indications of severe renal failure. In Table I it can be noted that a trend toward a slight rise in the 24 hour urinary volume was noted beyond the first week. This elevated volume, which did not exceed 1,000 c.c. in any case, was especially noted after 10 days. The impression was gained that the slight elevation in urinary flow corresponded to the slight elevations noted in the severe recoverable types during the prediuretic period between the fifth and twelfth days. From a theoretical view, projection of this curve of urinary volume forward would indicate a possible diuresis in 20 to 35 days.

All patients exhibited an oliguria of less than 100 c.c. for 3 or more days during the early period of renal failure. The specific gravity of the urine remained depressed throughout (range 1.006 to 1.010). Casts, white blood cells, and erythrocytes were noted early and a mild albuminuria was common throughout the course.

5. *Hypertension.*—A common feature of this syndrome has been hypertension. Whereas hypertension has been noted frequently in the recoverable type of tubular nephropathy (lower nephron nephrosis), its level has been variable, and the most common degree of hypertension has been mild, usually in the vicinity of 140/90 mm. Hg in young adults. In all but 3 of these patients the diastolic pressure exceeded 90 mm. Hg, 1 of these patients being a child 9 years of age. As noted in Table I, the hypertension has shown a definite trend up to a variable maximum, for example, the highest pressures were noted in 5 patients whose values amounted to 210/130, 180/120, 210/105, 150/100 and 170/90 mm. Hg. The blood pressure reached its maximum during the first 8 days.

6. *Mental Disturbance.*—Mental disturbances have occurred with regularity, a feature in direct contrast to the common experience with the recoverable form of acute renal failure. Eight patients displayed mental abnormalities throughout a major portion of the clinical course. In 7 patients the mental disturbances became apparent within 5 days of the onset of renal failure. One patient remained mentally clear for 8 days. The other 2 patients displayed restlessness terminally. Drowsiness and a cloudy sensorium were present in all 8 patients.

In addition, 5 patients became markedly confused, irrational, and at times maniacal. Three patients had periodic episodes of loud screaming, followed by quiet, semicomatose intervals. Localizing neurologic signs were not observed.

7. *Diarrhea.*—Diarrhea was a prominent disturbance in 5 patients, the stools being watery and containing blood. Bulky, bloody stools, either reddish or black, were persistent in 3 patients.

8. *Respiratory Distress.*—This was pronounced in 5 patients. All of these patients exhibited pulmonary edema, as revealed by basal or generalized râles, at some interval during the first 10 days. Preceding and following the recession of the edema, tachypnea became prominent, as revealed in Table I. Digitalis was administered to 4 of these patients, following which the pulmonary edema improved. Dehydration by means of peritoneal irrigation was beneficial for the pulmonary edema but did not control the tachypnea. Cyanosis was evident during the bouts of pulmonary edema. The introduction of a bronchoscope or intratracheal catheter yielded a thin, bloody fluid but failed to relieve the respiratory distress.

These observations indicated a serious disturbance in the parenchyma of the lungs. It was not possible to be certain whether one was dealing primarily with acute left ventricular failure or with a widespread increased permeability of pulmonary capillaries, as in so-called "uremic pneumonitis." Post-mortem observations, as described elsewhere, supported the latter at least as a contributing influence toward the respiratory distress.

9. *Anemia.*—Anemia, which was observed in all patients, became more pronounced as the uremia progressed, as noted in Table I. Blood transfusions were administered at irregular intervals to all patients.

The characteristics of the anemia were not determined, with the exception of 1 patient whose renal failure was associated with a hemolytic anemia displaying hemoglobinemia and hemoglobinuria. The possibility that the progressive anemia represented the ultimate degree of hemodilution following hemorrhages cannot be overlooked. However, 6 patients, following the apparent cessation of blood loss and despite blood transfusions varying between 1,000 and 3,000 c.c., continued to display a definite anemia. Thus, the possibility of uremic factors being at play in the progression of the anemia was definite but their actual presence was not demonstrated.

10. *Death.*—The mode of demise was similar in this group of patients. Terminally, the blood pressure dropped to hypotensive levels, the respiratory distress became aggravated, a comatose state ensued or was aggravated, and the patient succumbed gradually. Three patients exhibited terminal convulsive seizures.

POST-MORTEM FINDINGS

Post-mortem examinations were performed on 8 of the 10 patients; in 1 of these, however, the examination was confined to the kidneys. Externally, all of these patients were well nourished and well developed in appearance. Two pa-

tients were jaundiced at the time of autopsy. No peripheral edema was detected. The main changes involved the kidneys but additional disturbances were noted in the lungs, liver, gastrointestinal tract, and brain.

TABLE II. PERTINENT FEATURES OF CASES REPORTED

CASE	SEX AND AGE	BACKGROUND FOR RENAL FAILURE	DURATION OF SHOCK	SURVIVAL (IN DAYS)
1	M, 45	Repair perforation of gastro-enterostomy; three days later, pyrogenic reaction to IV fluid, hyperthermia (109° F.), and shock	48 hours	9
2 (Peritoneal irrigation 9 days)	M, 21	Gunshot wound in abdomen with perforation of aorta followed by repair, 26 pints blood given[14]	10 to 12 hours	16
3 (Peritoneal irrigation 12 days)	M, 43	Stab wound in chest and abdomen with laceration of liver, bled for 2 days, deficiency AC globulin	12 to 24 hours (vacillating BP)	22
4 (Peritoneal irrigation 4 days)	F, 49	Hysterectomy and salpingo-oophorectomy with blood loss and hypotension, then 500 c.c. incompatible blood transfusion followed by prolonged shock[5]	24 hours	14
5	M, 24	Struck by automobile; arrived in shock, duration unknown—at least 6 hours	6 hours (?)	9
6	M, 32	Psychiatric patient with profound shock associated with the clinical appearance of water and salt deficit, toxicologic examination negative[8]	Unknown	9
7	F, 37	Pelvic operation associated with 500 c.c. of incompatible blood transfusion, hemorrhagic state	Shock not detected clinically	17
8 (Peritoneal irrigation 7½ days)	F, 30	Thoracoplasty with blood loss, received at least 1,000 c.c. of incompatible blood[5]	5 to 6 hours	15
9	F, 9	Hemoglobinemia and hemoglobinuria, arrived in shock and coma	Unknown	16
10	M, 60	Combined abdominoperineal resection, incompatible transfusion, shock[2]	6 to 12 hours	16

Kidneys.—The kidneys were large, flabby, soft, and pale. They were heavy (average combined weight 430 Gm., range 310 to 600 Gm.). The capsule stripped easily, leaving a smooth surface. The cut edges everted prominently. The cortex and medulla were poorly differentiated. The cut surface had a mottled yellowish gray appearance. Microscopically, the glomeruli were intact and unaltered except for the occasional presence of a proteinaceous precipitate in the capsular spaces. The entire tubule was altered. The involvement of the distal segment of the tubule was more pronounced than that of the proximal segment. The latter, however, was altered in all cases; in 6 of the 8 cases the changes were of an advanced type.

The proximal segments (convolutions) were dilated and filled with a granular debris within which there were varying numbers of desquamated

epithelial cells. Focal necrosis involved either the entire circumference of the tubule or groups of 2 to 4 cells. The epithelium was flattened and often displayed a variation in the width of the cytoplasm, some zones being endothelial-like while others were moderately thick. The brush border was absent in the narrow areas but could be identified in the thicker zones. The wider cells often displayed a vacuolated cytoplasm. The nuclei of the cells varied in size and chromatin content, at times being hyperchromatic. An increased number of nuclei were often present and multinucleated cells were encountered. Mitotic figures were rare. This nuclear activity was prominent in 6 of the 8 cases.

The distal segments (convolutions) showed a greater magnitude of similar changes. Granular casts, which varied from a deeply eosinophilic to a light brown color, were common. Frequently a collar of desquamated epithelium could be identified about a contracted cast. Beyond the desquamated epithelium the tubule was usually lined by a flattened epithelium. Desquamation was common at this level. Disrupted tubules were surrounded by inflammatory cells, mainly macrophages and lymphocytes. Tubulovenous connections were readily observed.

The collecting tubules contained casts and remnants of the desquamated epithelium.

The blood vessels were unaltered in all but 1 case which displayed an apparently unrelated mild benign arteriolarsclerosis.

The changes described were observed in all cases regardless of duration of survival, for instance the kidneys from the patient surviving 22 days showed these changes. The flattened epithelium and nuclear activity were more pronounced in those patients surviving longer intervals (14 to 22 days). Thus, tubular regeneration was well advanced in all of these cases.

Lungs.—The combined weights of the lungs varied considerably, 640 to 1,320 Gm. (average 900 Gm.). The variation apparently resulted from the varying degrees of edema. Six cases revealed a characterisetic microscopic pattern. The edema fluid in the alveoli was rich in fibrin, the fibrin frequently forming plugs within the alveolar spaces. Scattered capillary hemorrhages were present. The alveolar walls were thickened due to hyperemia and the interstitial collection of inflammatory cells, neutrophils, lymphocytes, and macrophages. In the more advanced stages the fibrin plug changed into a rounded and hyaline mass partly filling the alveolar space. These changes conform with the lesion, termed fibrinous alveolitis, which has been considered to be uremic in origin.[9] Bronchopneumonia was also encountered in 2 cases. In another case, the patient had advanced tuberculosis.

Heart.—One patient with a history of rheumatic heart disease had a hypertrophied heart (weight, 540 Gm.). The other hearts were at the upper limits of normal in weight or slightly over (315 to 390 Gm.). Fibrinous pericarditis was encountered on one occasion. Subendocardial hemorrhages were observed in 2 other hearts. Two hearts revealed focal granular necrosis. One of

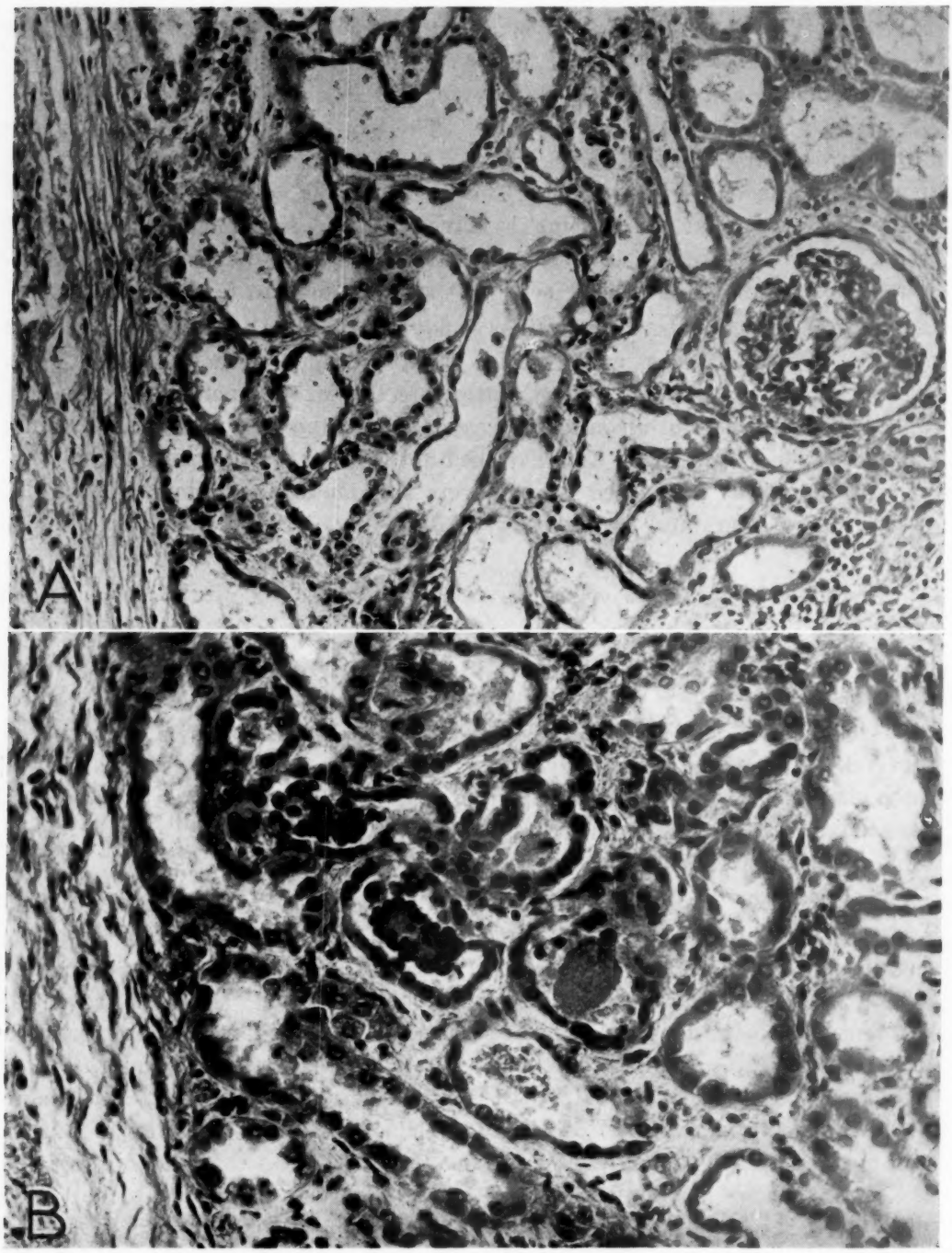

Fig. 1, *A* and *B*.—A (×190) (Case 4 [all case numbers refer to Table II]), A section of the kidney near the capsule showing an intact glomerulus and altered tubules. The tubules are dilated, partly filled with granular debris and desquamated cells and lined by a narrowed and flat epithelium. Increased numbers of nuclei, hyperchromatism, and variations of the nuclei are depicted. Both upper and lower segments are involved.

B (×200) (Case 7), A section of the kidney near the capsule. Changes similar to those mentioned under *A* are shown. In addition, contracted granular casts surrounded by a mantle of desquamated epithelium are shown.

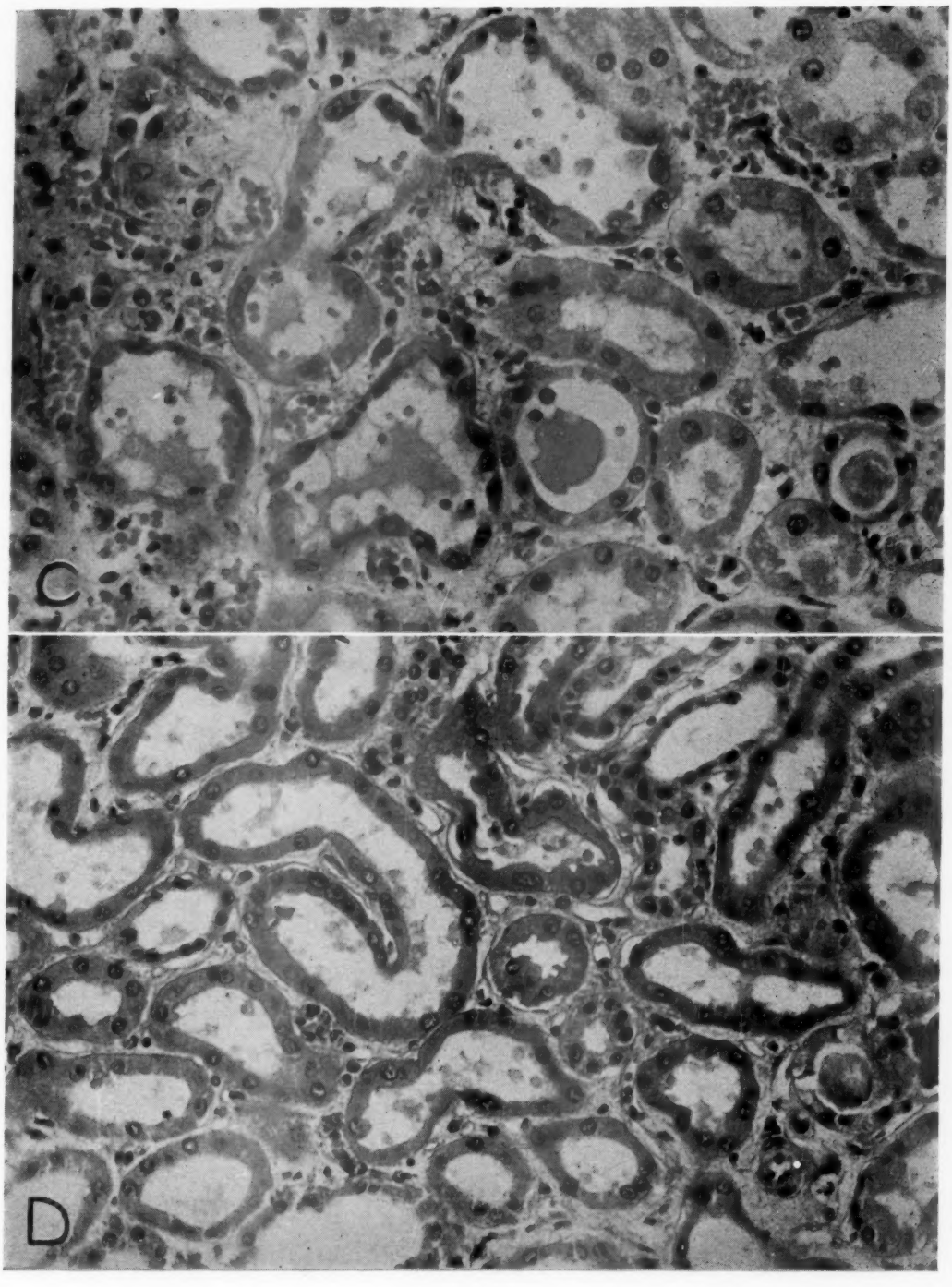

Fig. 1, *C* and *D*.—*C* (×425) (Case 6), Irregularly flattened epithelium and irregular hyperchromatic nuclei of the proximal convolutions are demonstrated. The thicker cells reveal the brush border.

D (×350) (Case 5), Dilatation, flattened epithelium, increased numbers of nuclei, and irregularity of the nuclei of both upper and lower segments are demonstrated.

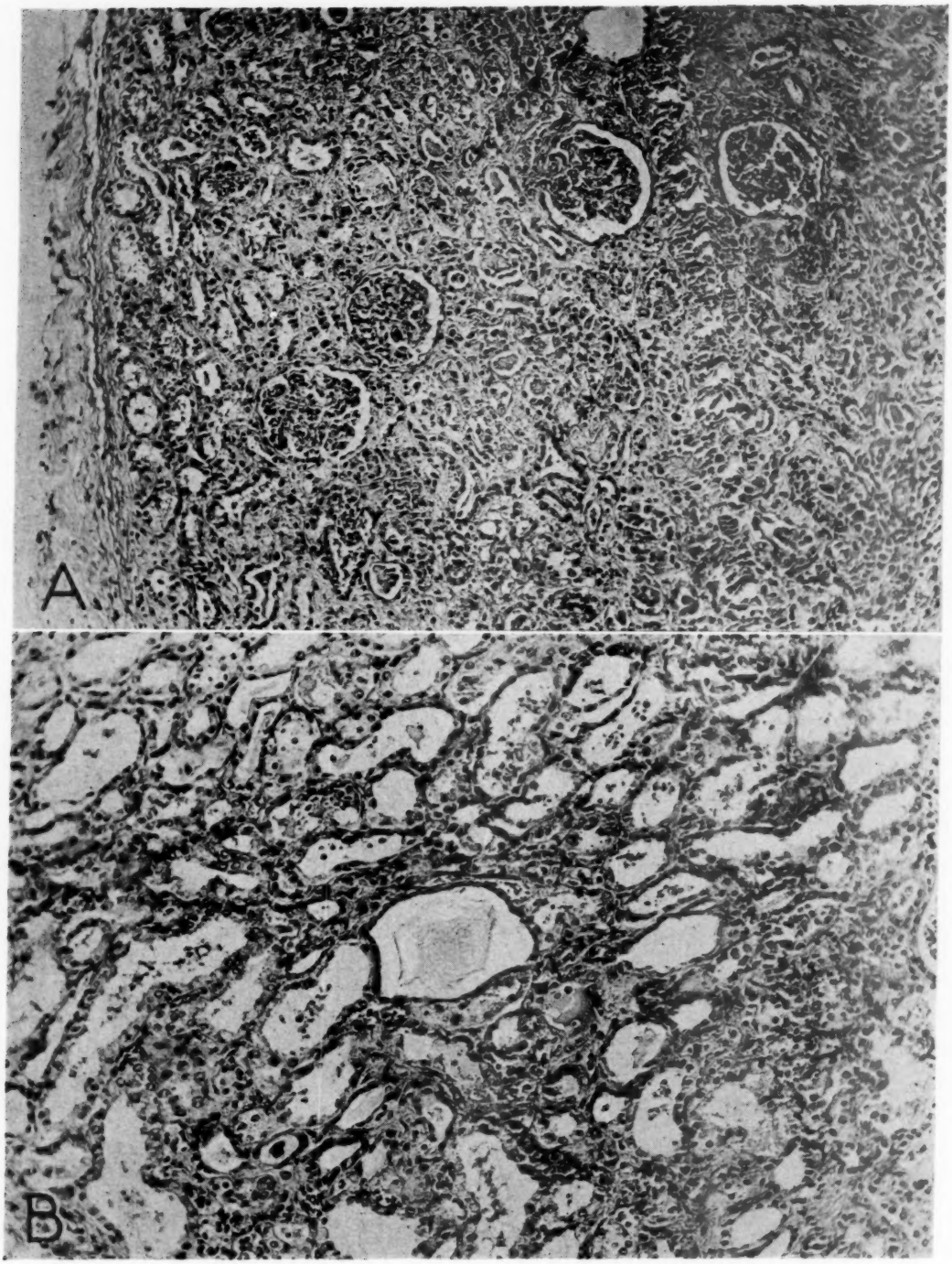

Fig. 2, *A* and *B*.—*A* (×140) (Case 3), Four normal glomeruli are shown. Between these glomeruli the tubules are necrotic (granular, disorganized, and mostly devoid of nuclei). Elsewhere serious tubular damage involving all segments is shown.

B (×190) (Case 3), The same kidney as in A showing in this area dilated tubules composed of flat epithelium.

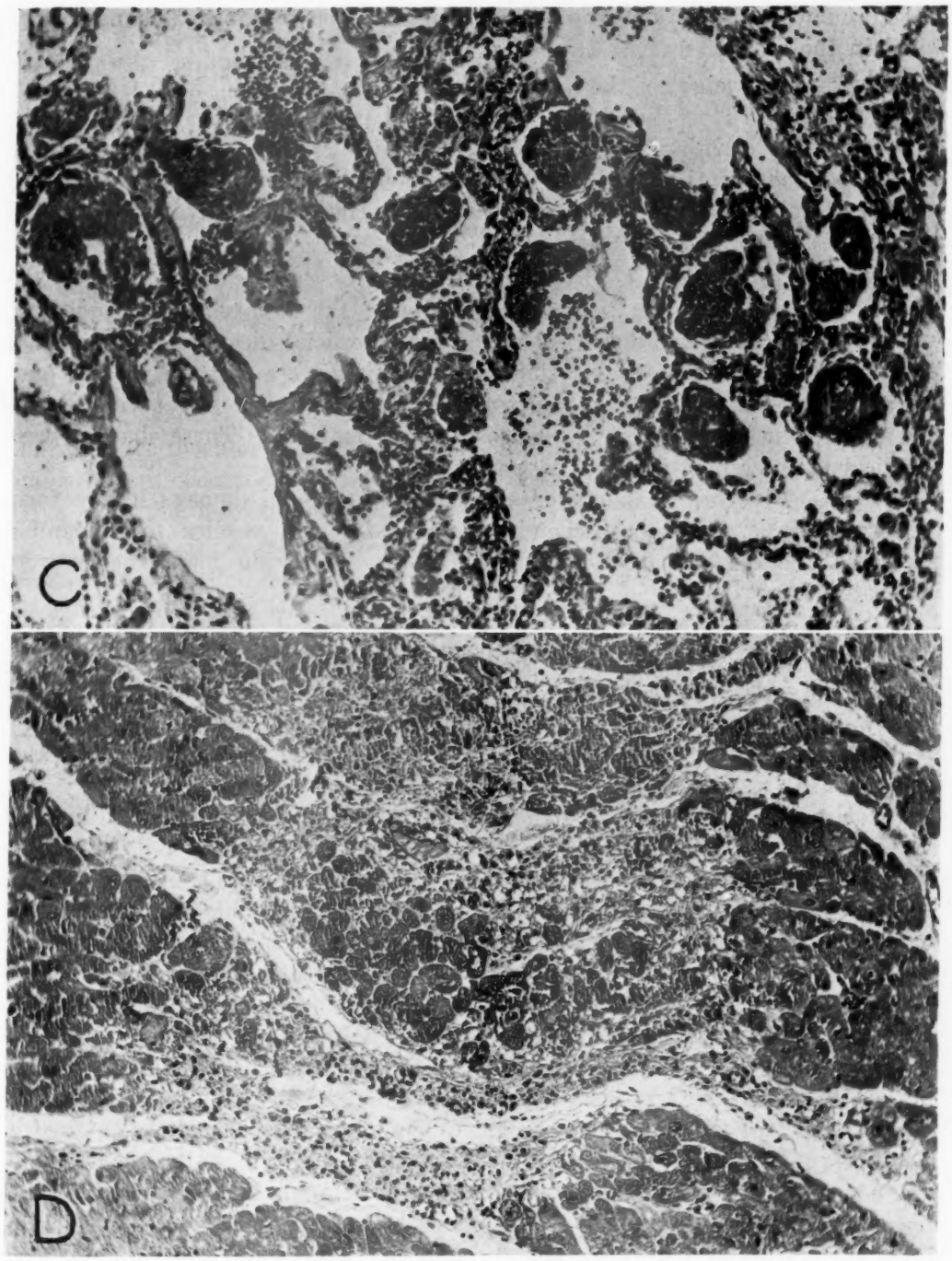

Fig. 2, *C* and *D*.—*C* (×170) (Case 3), The lung has many condensed fibrin plugs in the alveolar spaces. The alveolar walls have inflammatory cells. Scattered hemorrhages have occurred.

D (×160) (Case 3), The heart shows a focus of necrosis partly replaced by a young scar. Necrotic fibers remain within the scar.

these, from the patient surviving 22 days, also displayed multiple early scars and granulation tissue replacing the necrotic foci. No significant changes were noted in the other cases.

Liver.—The weight of the liver varied between 1,350 and 2,240 Gm. (average 1,860 Gm.). Thus, the livers were of about normal sizes and weights. Six of seven livers examined microscopically revealed evidence of damage to the central portions of the lobules. The centrolobular damages included central collapse, fibrosis, and hemosiderosis; central dissociation and advanced atrophy; and central fatty metamorphosis.

Gastrointestinal Tract.—Five of the seven cases revealed edema of the bowel. Hyperemia of the mucosa, especially of the stomach and duodenum, was common. Two cases displayed numerous superficial ulcers of the small and large bowel. In one of these, submucosal arteries were necrotic.[8] The pancreases from 5 cases showed atrophy of the acini and small ducts with distension due to the accumulation of an eosinophilic material. These changes were identical to those described by Baggentoss.[10]

Brain.—Five brains displayed evidence of nerve-cell damage in the form of chromatolysis, pyknosis, eccentric nuclei, karyolysis, swollen nuclei, and a prominent degree of satellitosis. In addition, focal-ring hemorrhages were encountered.

Additional Findings.—One patient had a perforated gastroenterostomy and local peritonitis. Another patient had advanced pulmonary tuberculosis at the time of the renal failure. A third patient revealed multiple infarcts of one kidney due to intrarenal thrombosis secondary to violent trauma in this area, while the remainder of this kidney and the other kidney in its entirety revealed the universal tubular nephropathy.

Comment.—The kidneys of these cases revealed a definite involvement of the entire tubule, that is, an upper and lower nephron nephrosis. At the time of autopsy, 9 to 22 days after the onset of the renal failure, regeneration was well advanced as evidenced by the replacement of desquamated epithelium by a flattened epithelium and the nuclear activity (hyperchromatism, variation of size, and multinucleation or "nucleosis"). Thus, death supervened while the kidneys were progressing morphologically toward recovery. The functional impairment was still advanced. Two organs, the brain and the liver, displayed changes which can probably be ascribed to advanced peripheral circulatory failure. The nerve-cell bodies of the cerebral cortex and other gray tissue were degenerated and partly phagocytized. Centrolobular hepatic damage, such as was observed in these cases, occurs when shock is severe and prolonged.[11, 12] The edema and inflammation in the lungs were of a special type, being characterized by much fibrin intra-alveolarly and the interstitial accumulation of inflammatory cells. This combination has been considered to be due to uremia (uremic pneumonitis?).[9]

DISCUSSION

The cases reported here are considered to represent a special variant of acute renal failure due to tubular damage.

The antecedent setting for the renal failure was a prolonged interval of peripheral circulatory failure, with or without hemoglobinuria. The administration of blood, plasma, and crystalloid solutions was attended by a transient or a partial improvement of the circulation, most patients being in and out of a hypotensive state for 12 to 48 hours. Thus the shock, which was prevented from entering into an immediately irreversible level, was of a slowly regressing sublethal type.

The renal failure differed in several respects from the recoverable form of "lower nephron nephrosis." The oliguria was extreme for intervals up to 22 days, the azotemia was high and fixed, and acidosis was severe and difficult to combat. In addition, widespread disturbances developed which included hypertension, diarrhea, mental aberrations, respiratory distress, and anemia.

Improvement of the chemical state of the blood was accomplished on four occasions by means of peritoneal irrigation, which was conducted for 4, 7½, 9, and 12 consecutive days, respectively. The azotemia abated by 50 per cent or more, the hypochloremia was relieved, and the acidosis improved. Clinical improvement occurred for a few days but death intervened at 14, 15, 16, and 22 days after the onset of the renal failure.

Morphologically, the kidneys have displayed an advanced universal tubular damage (upper and lower nephron nephrosis) which at the time of autopsy revealed evidence of considerable regeneration of both upper and lower segments. The lungs were the seat of a diffuse pneumonitis (fibrinous alveolitis and interstitial pneumonitis). The liver showed evidence of serious damage to the centers of the lobules. The brain revealed evidence of degeneration of nerve-cell bodies.

There were two major disturbances in these patients, namely, shock and uremia. It appears plausible, from present knowledge, to consider the shock as the cause of the widespread tissue injury including the nephropathy, the cerebral, hepatic, and possibly, to a certain extent, the pulmonary damage. The question of fundamental importance is whether the shock was the main lethal factor or whether uremia by itself or in combination with the shock constituted the main cause of death. There is no clear-cut means of resolving these two considerations at present. By considering shock as the main cause of death one assumes that a delayed noncirculatory irreversibility occurred as the result of the widespread tissue damage. There is precedence for this assumption, as in the fatal cerebral decortication following a reversible, prolonged, cardiac standstill in which death may not occur for 10 to 15 days. This interpretation allows for no therapeutic outlook.

Should the uremia, by itself, or in combination with the shock, be a necessary lethal requisite, then the therapeutic outlook is altered. There is ample morphologic evidence of renal recovery. Functionally, the minimal increments in the daily urinary volume flow occurring after 10 days offer some degree of hope for renal recovery. The question is whether the proper control of the uremia over a prolonged period by extrarenal measures will extend survival into a period of renal recovery. The indications are that 30 to 40 days of sur-

vival may be required to test this possibility. Thus, it is in this type of acute renal failure that the artificial kidney and peritoneal irrigation have their main indications.

The group of cases described here is not extremely uncommon in civilian practice for, in our experience, it represents approximately 10 per cent of patients with acute renal failure due primarily to tubular damage observed in a general hospital. In times of military strife the incidence of this type of renal failure is expected to increase, which may account, in part, for the higher mortality for acute renal failure recorded during World War II, as compared to the postwar civilian experience.

Clinically, it is difficult to differentiate the acute renal failure due to advanced universal tubular damage (upper and lower nephron nephrosis) from bilateral (symmetrical) renal cortical necrosis, whereas morphologically the separation is readily made.

SUMMARY

Prolonged and profound peripheral circulatory failure (shock), possibly modified by blood transfusions and crystalloid infusions, is associated with the developement of a nephropathy characterized by serious damage to the upper and lower renal tubular segments and an acute progressive unrelenting renal failure. The renal failure is associated with a prominent hypertension, mental aberrations, respiratory distress, diarrhea, and a persistent anemia. All approaches toward the management of the uremia thus far, including the use of peritoneal irrigation, have failed. Evidence of widespread tissue damage has been noted in post-mortem examinations.

Of fundamental importance is the question of whether shock per se is the lethal factor or whether the uremia is a requisite in the cause of death. In view of the latter possibility it is considered that this type of case represents a great challenge for the procedures designed to remove waste products from the body and alleviate the uremic state.

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SURGICAL APPLICATIONS OF AN INTRA-ARTERIAL TRANSFUSION APPARATUS

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THE majority of surgical procedures are today performed with adequate control of blood loss, and replacement with whole blood intravenously is the most simple and preferred method. However, a small number of operations still are complicated by an exsanguinating spontaneous internal hemorrhage or some other massive blood loss, and continue to present a grave surgical problem.

To reduce this hazard, a number of institutions in the United States now occasionally employ the arterial infusion of whole blood as a procedure designed to cope partially with this trying situation. Too, the ever present "surgical shock" factor inherent in the more radical cancer operations often creates, or makes imminent, a need for arterial transfusions. Under such circumstances, a preventative, or "in readiness," fashion of thinking seems consistent with many other current ideas designed to anticipate and avoid catastrophes rather than rely on makeshift emergency devices.

Certain earlier concepts of hemorrhagic shock contended that a fundamental physiologic response during shock was a sustained peripheral vascular collapse, with the heart somehow maintaining a normal state. This type of reasoning clouded the entire picture of shock treatment, for it led to the conclusion that a drug which would constrict the vascular bed was adequate therapy when combined with intravenous blood transfusion.

In 1942, Wiggers and Werle[22] demonstrated in canine experiments that a marked reduction in cardiac muscle efficiency accompanies prolonged hemorrhagic shock. These investigators found the stroke volume of a dog's heart reduced as much as 70 per cent by a severe shock state. The capacity of the ventricles to respond to a given pressure (stretch of the muscle) was markedly reduced. They concluded an impairment of coronary blood flow was probably responsible for this phenomenon.

Subsequent investigations by Page and Abel[13] indicated that a contraction of arteries and arterioles occurs early in hemorrhagic shock, but that prolonging the shock state led terminally to vascular relaxation. The latter is probably a prominent feature of the terminal stage of shock, or the irreversible shock state. The mandate to overcome the hypotensive state by some appropriate means (i.e., arterial transfusion) is clear. Reduced heart size was also noted early in shock, with a subsequent enlargement of the heart during the terminal stages.[10] Perfusion of veins with blood after the heart had started to enlarge seemed to hasten death of the experimental animals. Observations of this type foretold the advent of arterial infusion of blood in hemorrhagic shock, for by

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artificially boosting the blood pressure via arterial infusions one might prevent the effects of hypoxia on the myocardium due to prolonged reduction in coronary flow.

Animal experiments during the past eight years have well established the efficacy of arterial blood replacement in the treatment of large blood losses. Simple bleeding experiments,[6, 7] with maintenance of a shock state in groups of dogs for varying lengths of time, demonstrate that arterial replacement of the volume of blood lost will save more animals than intravenous replacement of similar volumes of shed blood. The venous pressure can rise quickly to dangerous levels when large volumes of blood are given rapidly by vein if a shock state has existed for some interval. Pulmonary congestion and edema have been produced in profoundly shocked dogs by rapid intravenous blood infusions.[2] Eaton[2] identifies this phenomenon with a relative anoxia induced by hypotension in the pulmonary circulation causing metabolic trauma to the cells of the intima of the alveoli, and thereby increasing the permeability of these membranes.

Robertson, Trinker, and Dennis, in 1948,[15] reported their plethysmographic measurements of blood flow to a dog's extremity during shock and during various types of treatment. Initially the plethysmographically measured blood flow to the extremity was markedly reduced after withdrawal of blood from another artery, and despite only a minimal concomitant fall in arterial pressure. After 30 to 75 minutes in a hypotensive state, the reinfusion arterially of volumes of blood equivalent to those bled off restored the blood pressure within the arterial bed to approximately normal values. In addition, the blood flow, as indicated by the plethysmograph, was almost normal in 4 to 7 minutes. Intravenous blood transfusion took four times as long to return blood pressure and blood flow to prebleeding levels.[45] They[15] also pointed to the appearance of right heart congestion when intravenous blood replacement in a bled-out, markedly hypotensive animal exceeded 20 to 25 c.c. per minute.

Stead and Warren[20] have emphasized the importance of adequate capillary circulation in the maintenance of normal metabolic processes in the body generally. They consider a prolonged impairment of circulation a prime mechanism in the production of metabolic abnormalities, changes which rapidly may become irreversible and lead to death. Cardiac cells, they noted, were among those damaged early; therefore, an elevation of the venous pressure by massive intravenous blood transfusion may insult an already failing myocardium. Also, during early shock states, when the peripheral resistance is increased due to arteriolar constriction, and organs and tissues become relatively ischemic, the kidney is affected by hypoxia along with other vital organs. This can produce a renal effect simulating the prelude of the crush syndrome.[12] On the other hand, with an elevation of the arterial pressure by an arterial transfusion sufficient to force blood through these constricted arteriolar beds, the normal physiologic response of the arterioles to increased intraluminal pressure relaxes the vessels and they pass blood more readily.

Fine, Frank, and Seligman[3] consider the restoration of blood volume the most urgent feature of treatment in hemorrhagic shock. Their studies with a

crossed infusion of blood from a normal donor dog, through the portal vein of a "shocked" recipient dog, demonstrate that perfusion of the liver during the interval of shock will enable a dog to recover from otherwise irreversible shock. The handling of metabolites proceeds in a more normal manner during the shock state if adequate blood flow through the liver is maintained. Their conclusion is that irreversibility of the shock state is a functon of the severity and duration of inadequate capillary flow to peripheral tissues as well as vital organs. By rapidly raising the intra-arterial pressure with arterial infusion of blood, the dangers of the irreversible shock state are lessened.

REQUIREMENTS AND CRITERIA OF ARTERIAL TRANSFUSION EQUIPMENT

Certain minimum standards were recognized and built into the original arterial equipment. From our experience of several years' use of this type of transfusion instrument, the following qualifications have assumed increasing importance: (1) constant pressure source with a simple, adjustable, valvular regulator for a broad swing in pressure gradients, (2) ease and certainty of sterilization for all parts, (3) uniform filtration of blood prior to infusion, (4) safety devices prohibiting gas emboli.

The regulating valve (*A* in Fig. 1) is an argon therapy reducing valve. Reflux from the patient into the machine is prevented by a ball-type valve (*B* in Fig. 1) made of clear Lucite. The distribution valves (*E* and *F* in Fig. 1) are stainless steel, three-way stopcocks. Stainless steel fittings on the blood valve (*F* in Fig. 1) permit rapid, tight connection of Polythene tubing to the stainless steel tubing.

The chrome pressure head unit (*G* in Fig. 1) rests on a bracket mounted on the front surface of the machine base. Pressure oxygen fittings (1 in Fig. 1) from the oxygen distribution valve can be screwed into place quickly. The filtration chamber (*2* in Fig. 1) in the head unit, distal to the oxygen attachments, cleanses the oxygen before it reaches the blood. The blood cannisters are held in place on the head unit by small brackets shaped like a foot (*3* in Fig. 1) which swing into or out of position as the wing nuts on top of the head casting are turned. Stainless steel shutoff valves (*I* in Fig. 1) are permanently fastened to the lower end of stainless steel tubes which carry blood from the bottom of the cannisters. Plastic cannisters (*H* in Fig. 1) are made of clear Lucite, calibrated in 100 c.c. increments, and have a capacity of 800 c.c. The shutoff valve closes as the cannister is withdrawn and prevents air from entering the system.

The plastic drip flow filter unit (*J* in Fig. 1) can be disassembled in the middle and the only communication between the upper, or drip chamber, and the lower, or reservoir chamber, is through the fine stainless steel mesh. Distance between strands of this mesh is 0.009 inch, and is effective in removing tiny fibrin clots. A small stopcock in the top of the drip chamber enables the level in the reservoir to be raised or lowered at will by releasing air to raise the level, or by injecting air with a syringe to depress the level. Filters can be changed during the operation of the machine. The central column of the

base is adjustable for height, permitting the level of the blood to be adjusted to the level of the patient's heart; a necessary arrangement if blood pressure readings are to be taken on the manometer of the machine.

An orderly procedure enables a trained person to set the machine up ready for use in five minutes. The autoclave pack includes the head unit with the shut-off valves, the fluid three-way stopcock, the needle adapter, three extra filters, and an assortment of Lindeman needles. The plastic pieces along with the various Polythene tubings are washed in detergent, rinsed, and deep-tank sterilized for at least 2 hours in aqueous Zephiran and 2 per cent formalin.*

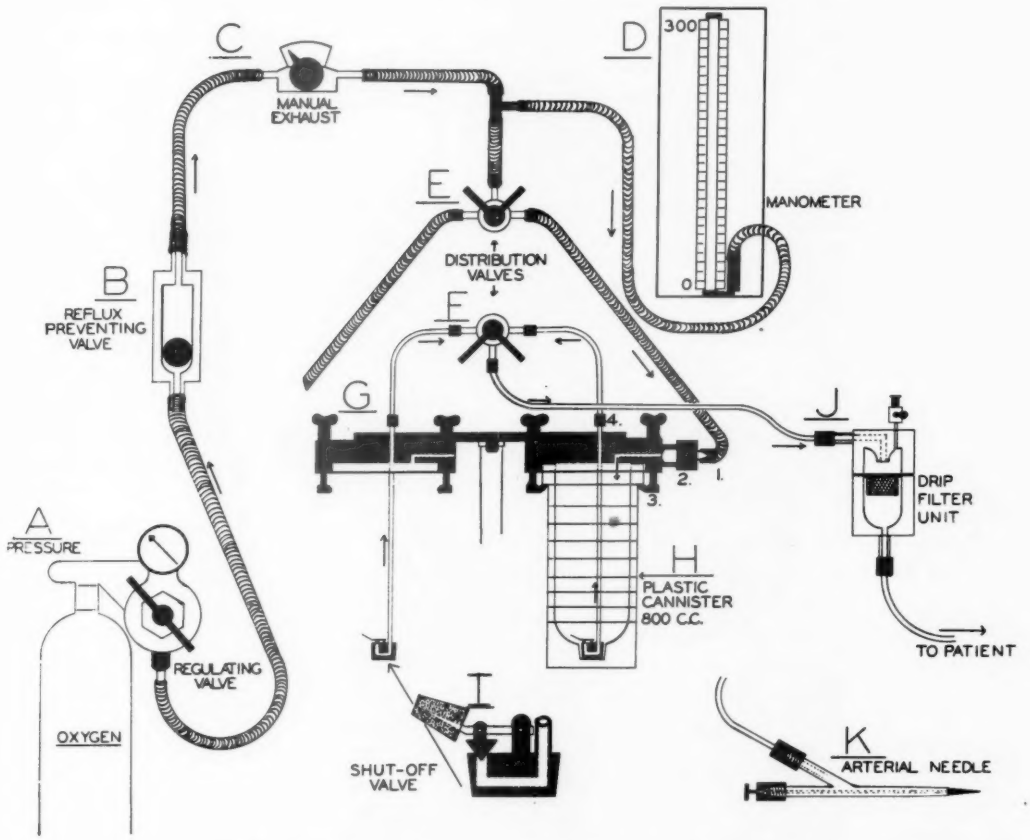

Fig. 1.—Scheme of flow through intra-arterial transfusion machine: *A*, oxygen pressure tank and regulating valve, *B*, reflux prevention valve, *C*, manual exhaust, *D*, mercury manometer, *E*, and *F*, distribution valves, *G*, pressure head unit, (*1* airtight fittings, *2* filtration chamber, *3* wing nut foot fasteners, *4* special attachment for Polythene), *H*, plastic cannister, *I*, shutoff valve, *J*, drip filter unit, *K*, arterial needle.

They are then rinsed with sterile distilled water and wiped dry by a gowned and gloved nurse. Wrapping in a previously autoclaved plain-tray pack completes the procedure. Studies in our laboratories using rabbits as the test animal have shown these sterilization methods to yield a pyrogen-free infusion. The use of formalin to sterilize spore forms has been tested on equipment made for dog perfusion experiments and no unsatisfactory results have occurred.

*An aldehyde test developed by Mr. O. W. Sletten of the Coca-Cola Company of Minnesota was used to determine freedom of rinsed and sterile plastic pieces from adhering formaldehyde.

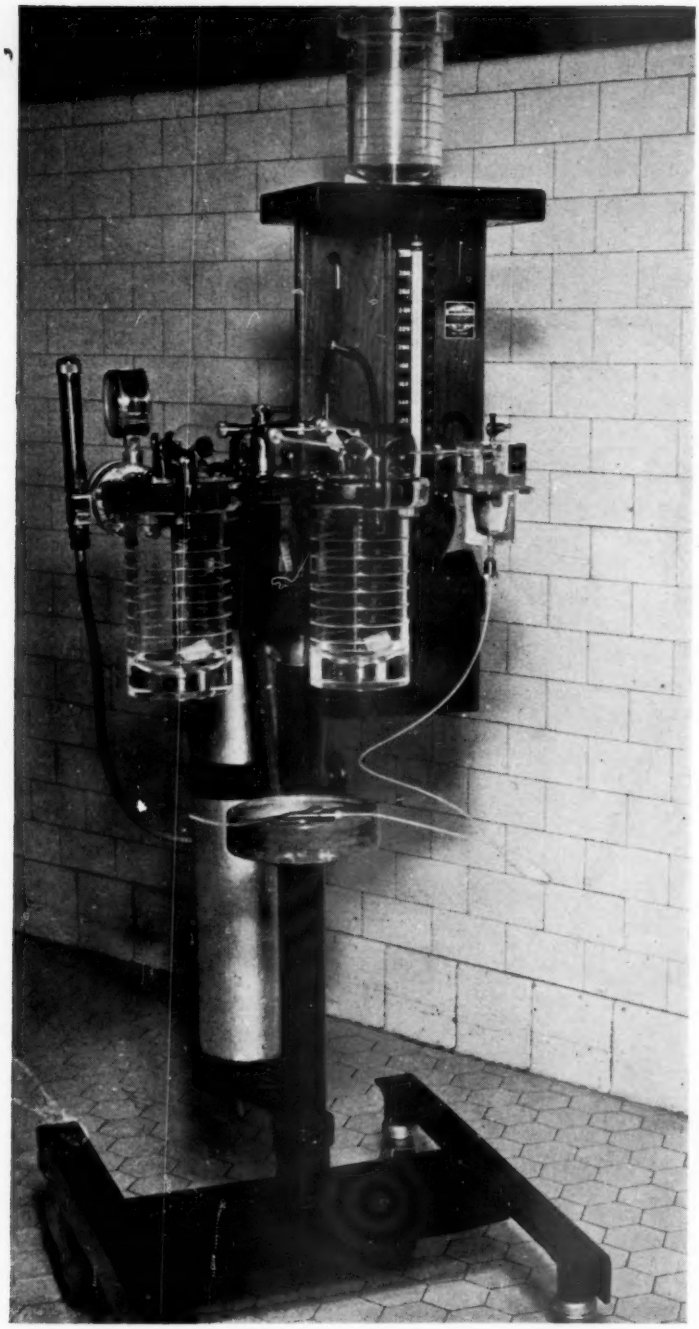

Fig. 2.—Assembled intra-arterial machine.

FUNCTIONS AND CLINICAL USE OF THE MACHINE

We have used the infusion equipment to advantage in eighteen patients within the past twenty-four months. In the clinical experience, 300 to 500 c.c. of blood, given in three or four minutes, customarily has been effective in raising the blood pressure above 100 mm. Hg. When required, the flow can be speeded up, but this relatively small quantity of blood necessary to improve the circulatory dynamics in a hypotensive patient is one of the striking features of using the arterial route for blood replacement. We have noted that the blood pressure of the patient will immediately fall, after this initial rise, if adequate intra-arterial flow is not maintained until the blood volume has been restored toward normal. On certain occasions it was necessary to infuse blood into a femoral artery for several hours during an interval while hemostasis was difficult to achieve.

CASE 1 (U. H. 796798).—Patient G. L., a 49-year-old man, had a gastrectomy in April, 1949, for carcinoma of the stomach. He was asymptomatic until December, 1949, and was then re-explored in a second look for cancer metastases. Liver metastases were found and removed. The patient developed intraperitoneal bleeding in the recovery room about four hours after closure, and intravenous blood pumped into three extremities did not raise his blood pressure. At the start of the intra-arterial infusion the blood pressure was less than 50 mm. Hg, and the pulse was unobtainable. The blood pressure rose to 100 mm. Hg in five minutes after 300 c.c. of blood had been given under a pressure of 300 mm. Hg. The rate of infusion was then slowed and the pressure slowly rose to 110 mm. Hg. Surgery was performed and re-exploration revealed a rent in the portal vein which was successfully closed. A total of 2,000 c.c. whole blood was given intra-arterially and the patient's blood pressure was 120 on returning to the ward. In this case, a Polythene tubing (1.5 mm. inside diameter) was used and was threaded through the special side-arm needle that remained in the vessel during the infusion. There was no leakage around the needle and three stitches of 000000 silk were used for transverse closure of the defect in the artery. The patient left the hospital on the seventh postoperative day with adequate circulation to the left leg. This patient demonstrated the usefulness of the femoral artery as the site of infusion, and the rapid rise of blood pressure with relatively small quantities of blood into a major artery.

CASE 2 (U. H. 812242).—Patient R. S., a 22-year-old man, had a large tumor mass in the left upper quadrant; at operation it was found to involve the spleen, left kidney, splenic flexure of the colon, and several loops of ileum. It encroached intimately upon the aorta for a considerable distance. The tumor mass was a carcinoma of the cortex of the left kidney, and early in the en bloc removal of all the structures in this area the blood pressure dropped to 75 mm. Hg. This amount of shock plus the potential hazard of severe hemorrhage from the aorta during dissection stimulated the surgeon to use the arterial infusion machine. A 1½ mm. (inside diameter) Polythene tube was secured in the left femoral artery with a purse-string suture and 350 c.c. of blood given in five minutes, under a differential pressure of 300 mm. Hg. The blood pressure of the patient was 100 mm. Hg after this amount of blood had been infused. The surgery was continued successfully. Several other pressure drops due to excessive blood loss occurred, but at these moments the flow in the machine had been slowed down. Speeding up the flow raised the pressure in each instance to 110 in two to three minutes. There was no residual difficulty in the circulation of the limb which received the Polythene tube into the femoral artery.

CASE 3.—(U. H. 801968).—G. L., a 60-year-old white man, had excision of metastatic tumor from the liver one year after colectomy and urinary cystectomy for carcinoma of the colon. The arterial infusion machine was connected to the left radial artery of the patient at onset of the operation. A slow drip was maintained until blood loss was encountered with removal of large segments of liver, then increased arterial flow immediately corrected a sudden blood pressure drop. The patient recovered without incident.

During a severe hypotensive state a reasonable working appraisal of the blood volume situation is obtainable from the patient's blood pressure coupled with weighed blood loss and the replacement total. The need for more precise periodic measurements of cardiac stroke output, total blood volume, and peripheral venous pressure are acknowledged. Until these become available, however, reliance is necessarily placed on several more indirect procedures. In the majority of cases blood may be given arterially until the blood pressure reaches the normal preoperative level, and then the flow can be adjusted at a slower rate to stabilize the pressure at that point. This has proved a satisfactory measure of the patient's need for blood, provided too severe hypotension did not exist for too prolonged a period of time.

This equipment also has been used in the experimental laboratories to provide a steady flow intra-arterially of various dissolved chemical mixtures for periods up to ten hours. Regional heparinization of an extremity could be performed simply and effectively through a peripheral artery with this equipment. Constant flow around the clock can be maintained with safety due to the automatic shutoff valves and lack of pump mechanism.

ANIMAL EXPERIMENTS

Experiments on dogs have examined the capacities of this equipment particularly for flow rate and for automaticity of operation. As would be predicted, the diameter of the Polythene tubing from the drip unit to the animal and the internal size of the trocar, or infusion needle, are limiting factors in the flow rate. Polythene tubing with an inside diameter of 2 mm. will deliver blood at a rate of 300 c.c. per minute, with the pressure on the machine set at 350 mm. Hg and with the pressure in the dog's artery 100 mm. Hg. In human patients, using Polythene tubing with an inside diameter of 3 mm. and a No. 13 Lindeman needle in the femoral artery, a flow rate in excess of 300 c.c. per minute was sustained for short periods of time when the differential pressure between the instrument and the patient ranged about 350 mm. Hg.

To test the effect of arterial infusion of blood on the pressure at the aortic arch, when the blood was given in the femoral artery, the following experiments with minor variations were performed:

In a 46 pound male dog anesthetized with 15 mg. pentobarbital per pound of body weight, the left carotid artery was exposed, connected to a mercury manometer by a Polythene tube threaded down to the aortic arch and zeroed to heart level. A 2 mm. inside diameter Polythene tube placed in the left femoral artery was threaded up to the aortic bifurcation; the arterial infusion machine was joined to the animal by this route. The right femoral artery was exposed and a 13 gauge needle inserted to obtain rapid bleeding from this vessel. The pressure on the manometer of the infusion machine was stabilized at 140 mm. Hg with a corresponding aortic arch pressure in the dog.

Coincident with the start of exsanguination from the right femoral artery the pressure on the blood in the arterial machine was raised to 350 mm. Hg. Subsequently, the blood pressure in the dog dropped to 70 mm. Hg but recovered

to 100 mm. Hg within forty seconds after aortic bleeding ended. Within the next sixty seconds, the arterial pressure had risen to 112 mm. Hg and stabilized there. The average flow rate for the four-minute period was 212 c.c. per minute, with a maximum of 300 c.c. per minute during the time of greatest differential. These experiments were repeated eight times on the same animal in close succession and the results were essentially similar in each instance.

SUMMARY

The intra-arterial replacement of blood has proved repeatedly advantageous in the shock therapy of patients suffering from severe hemorrhage. Cardiac function and arterial circulation appear improved when the blood pressure in the arterial tree is quickly and effectively raised from the hypotensive state. This clinical experience is in agreement with the experimental evidence demonstrating that the stroke output of the heart increases with the rise in blood pressure and that tissue perfusion improves with the rise of arteriolar pressure from shock level.

A semiautomatic machine for safely and rapidly perfusing arteries has been presented; the construction of the various parts is discussed in detail. Clinical experience has demonstrated improvement in patients in the reversible phase of hypotensive shock after three to five minutes of arterial infusion. Animal experiments demonstrate the immediate beneficial rise of blood pressure at the level of the aortic arch when blood is rapidly forced into the femoral artery under suitable pressure.

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EXPERIMENTAL ASCITES—ITS PRODUCTION AND CONTROL

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THE various methods used to produce ascites in experimental animals have been adequately described in excellent reviews, and the character of ascitic fluid and its variation has also been extensively investigated.[1-6] One of us (J. K. B.) previously described[7] the production of ascites by constriction of the superior vena cava above the diaphragm with the application of Polythene film.*

This report is based on observations of eighteen dogs made ascitic by occlusion of the inferior vena cava above the diaphragm. Our studies include morphologic and physiologic changes in the liver; analyses of ascitic fluid; and the effects of dietary measures, ligations of the hepatic, splenic, and celiac arteries, and portacaval shunts on the chemical characteristics and rate of production of ascites.

METHODS EMPLOYED IN THE PRODUCTION OF EXPERIMENTAL ASCITES

Group I.—We first attempted to produce ascites in the experimental animal by complete ligation of the portal vein caudad to the gastroduodenal vein so that the liver would receive portal blood via the cranial and caudal pancreaticoduodenal veins which anastomose with the caudal mesenteric vein. However, in spite of the administration of penicillin the dogs succumbed within forty-eight hours of liver necrosis. There was some ascites but mostly bloody fluid due to a rhexis of the smaller portal radicles.

Group II.—Three dogs were prepared by incomplete ligation of the portal vein with a Polythene band. Fluid accumulated in the peritoneal cavity in about six weeks but soon disappeared. In this group of animals the ascitic fluid was not influenced by the diet in spite of the fact that as much as 20 Gm. of salt were given per day. Increase in protein also did not influence the amount or character of the ascitic fluid.

Group III.—Twelve normal mongrel dogs weighing from 9 to 13 kilograms were selected and put on a stock diet.† The dogs were anesthetized with pento-

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*1.5 mm. type NB-7-14 DuPont.

†Stock Ration, Prepared by the Borden Company:

Crude protein, not less than	25.0%
Crude fat, not less than	5.5%
Crude fibre, not more than	5.0%
Ash, not more than	12.0%
Moisture, not more than	9.0%
Nitrogen-free extract, not less than	40.0%

Ingredients: Meat meal, flaked corn, soybean oil meal, corn germ meal, flaked wheat, fish meal, fish liver and glandular meal, dried whey solubles, rice polishings, dried beef pulp, dehydra'ed cheese, animal liver meal, ice cream cone meal, whole wheat germ meal, 2,000 U.S.P. units vitamin A, 450 U.S.P. units vitamin D, 1 mg. thiamine, 6 mg. riboflavin, 20.0 mg. niacin. One-half pound, mixed with an equal amount of water, is fed once daily. Approximate sodium content: 1 Gm.

barbital sodium given intraperitoneally, 30 mg. per kilogram of body weight. Oxygen was administered through an endotracheal tube by rhythmical bag inflation. Through an incision in the right ninth intercostal space the vena cava was easily dissected out and a ¼ inch Polythene band tied with two silk ligatures around the vessel constricting it to approximately 50 per cent of its normal diameter. This produced ascites in all animals within a period of four to seven weeks (see Fig. 1).

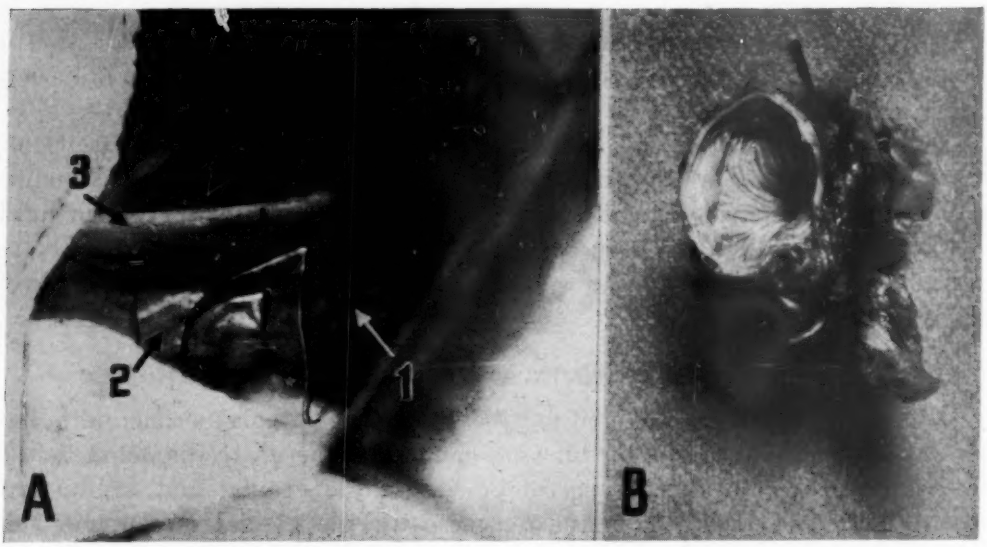

Fig. 1.—*A*, Polythene film in place around vena cava immediately above the diaphragm. *1*, Distal portion of vena cava. *2*, Two silk sutures sewed into the Polythene film and tied, constricting the lumen to about 50 per cent of its diameter. *3*, Phrenic nerve.

B, Photograph of inferior vena cava, proximal side, showing extreme constriction after three months.

EFFECTS OF INFERIOR VENA CAVA OCCLUSION

The animals produced approximately 2,000 to 3,000 c.c. of ascitic fluid every 2 weeks (see Fig. 2). Collaterals were apparent on the abdominal wall and intra-abdominally in the hepatogastric ligament and around the kidney pedicle, but no esophageal varices were detected either by inspection intraperitoneally or by esophagoscopy (see Fig. 3). The ascitic fluid was straw colored and its specific gravity was 1.016. The average chemical analyses were as follows: Total protein 3.2 Gm. per cent, albumin 1.4 Gm. per cent, globulin 1.8 Gm. per cent, chlorides 122 meq. per liter, sodium 157.8 meq. per liter, potassium 4.3 meq. per liter, cultures and smear negative, cell count 600 erythrocytes per cubic millimeter and 2,000 leukocytes per cubic millimeter, all of which were polymorphonuclears. Portal pressures were recorded in every animal and although pressures were not taken prior to caval ligation they were higher than those seen in normal dogs, ranging from 220 to 245 mm. of citrate solution. Liver function tests and blood studies gave the following results: prior to ligation

total protein averaged 6.1 Gm. per cent, albumin 3.7 Gm. per cent, and globulin 2.4 Gm. per cent. The average bromsulfalein retention at the end of 45 minutes was 5.1 per cent. Six weeks after vena caval occlusion the total proteins averaged 5.8 to 6.5 Gm. per cent, albumin 2.6 to 2.8 Gm. per cent, and globulin 3.2 to 3.7 Gm. per cent. Bromsulfalein retention varied from 5 per cent in 45 minutes to 16 per cent in 45 minutes; plasma sodium was 145.5 meq. to 158.1 meq. per liter. Biopsies of the liver showed a passive congestive type of liver

Fig. 2.—Photograph of dog B103 showing enormous accumulation of ascites three months after ligation of the inferior vena cava above the diaphragm.

necrosis (see Fig. 4) and fibroplasia (see Fig. 5). After ascites had been present for two to three weeks, plasma proteins began to fall and were greatly influenced by diet.

EFFECTS OF SODIUM AND PROTEIN INTAKE

Normal controls could be fed enormous quantities of salt in capsules up to 30 Gm. per day without producing ascites. Salt in the diet of animals made ascitic by the method described, in quantities of 10 Gm. per day increased the amount of ascites to 3,500 to 4,000 c.c. every two weeks. Ascitic fluid protein dropped to an average of 2 Gm. per cent. Plasma protein decreased to 3.6 Gm. per cent. When the animals were put on a high salt diet (10 Gm. per day) with copious quantities of water (1,000 c.c. per day by stomach tube) the rate of formation of ascites was not significantly altered. Water per se played little role in increasing the amount of ascites in animals on a high-protein, low-salt diet, or on stock rations.

The animals were then placed on a pure protein diet consisting of one pound of horse meat daily. This contains only 0.5 Gm. of sodium or about one-half as much sodium as is found in the stock ration previously described. It is very difficult to remove all of the sodium from the meat without dializing it after it has been finely ground, and when this is done the animals refuse to eat it. On the pure meat diet the ascites decreased to an average of 1,200 to 1,500 c.c. every two weeks. Plasma proteins rose to an average of 5.8 Gm. per cent and ascitic fluid protein to 3.2 Gm. per cent.

EFFECTS OF REVERSE ECK FISTULA

Portacaval shunts were done in three of the ascitic animals by side-to-side anastomosis. This produced an increase in the amount of fluid because in

Fig. 3.—Photograph of dog B207 showing ascites and enormous collateral formation in the abdominal wall. Note the extreme emaciation which followed repeated paracenteses without adequate protein replacement.

animals with a reverse Eck fistula, pressures in the inferior vena cava rise to levels higher than are normally present in the portal vein, thereby causing portal hypertension. These same animals were operated upon six weeks later and the hepatic artery tied. Two of the three animals died as a result of a clot forming at the juncture of the portal vein and inferior vena cava. The third dog formed more fluid, which was bloody, following this procedure and finally died with multiple infarcts in the liver.

EFFECTS OF LIGATIONS OF THE HEPATIC, SPLENIC, AND CELIAC ARTERIES

Ligation of the hepatic artery alone (three dogs) caused a decrease in the amount of ascites in dogs on stock rations from 2,000-3,000 c.c. to 500-600 c.c. every two weeks. One animal had a simple exploration as a control and the amount of ascitic fluid remained constant. A high-salt diet increased the amount of ascites proportionately (1,000 to 1,200 c.c. every two weeks) but not to levels which were reached prior to the ligation of the hepatic artery (3,500 to 4,000 c.c. every two weeks). A high-protein diet decreased the amount of ascites to 600 to 800 c.c. every two weeks. However, if 10 Gm. of salt were added to the daily intake, ascites increased to levels obtained with-

Fig. 4.

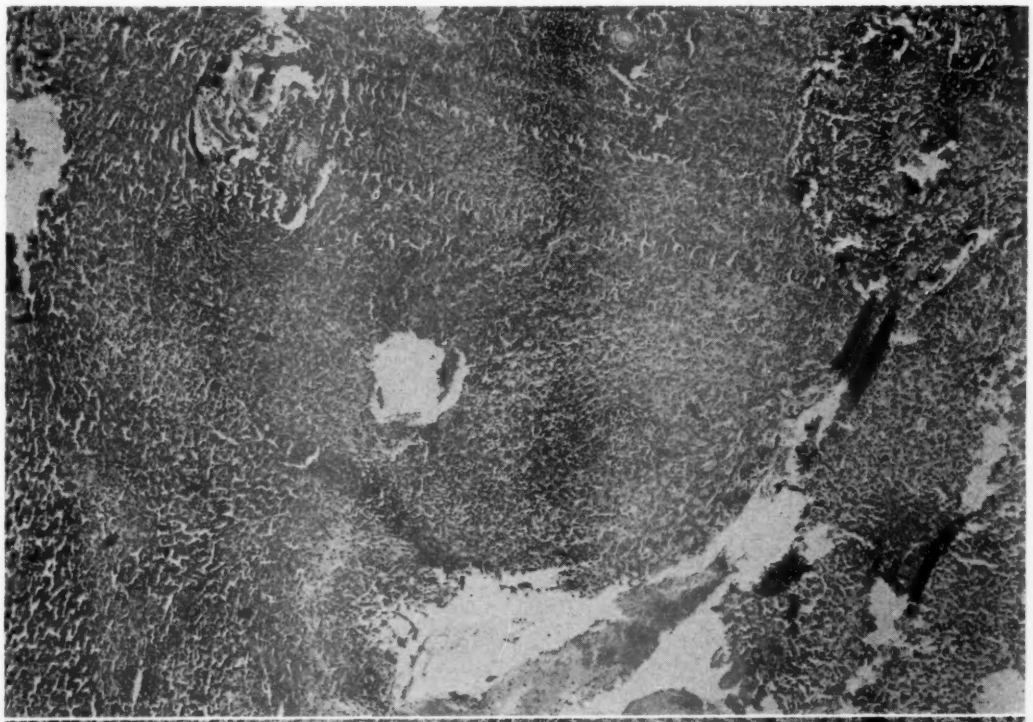

Fig. 5.

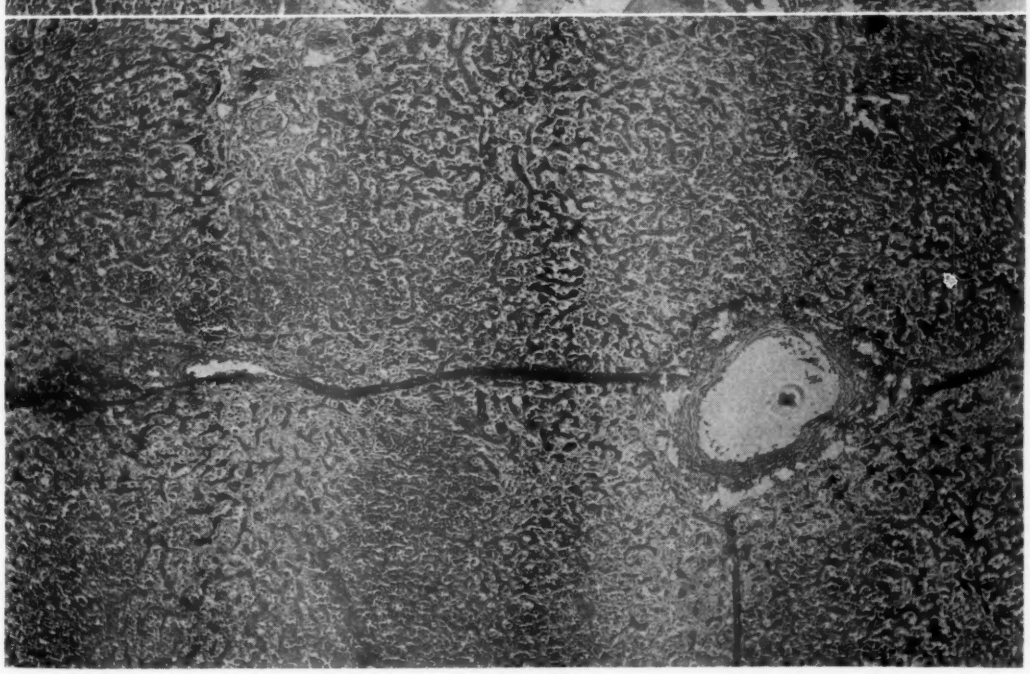

Fig. 4.—Photomicrograph (hematoxylin and eosin stain ×60) taken from the liver of dog B103 five months after partial ligation of the inferior vena cava with Polythene film. Note the areas of focal necrosis.

Fig. 5.—Photomicrograph (hematoxylin and eosin stain (×60) taken from the liver of dog B207 four weeks after partial vena cava ligation. Note the periportal fibrosis.

out a high-protein diet. Ligation of the hepatic and splenic arteries (3 dogs) decreased the ascitic fluid production even more (500 c.c. per month) (see Fig. 6). Again the amount and the quality of the fluid was altered somewhat by the diet as described. Ligation of the celiac axis (2 dogs) did not change the results. Animals observed for a year or more continued to form ascites in amounts of 500 to 600 c.c. per month when maintained on stock low-sodium rations.

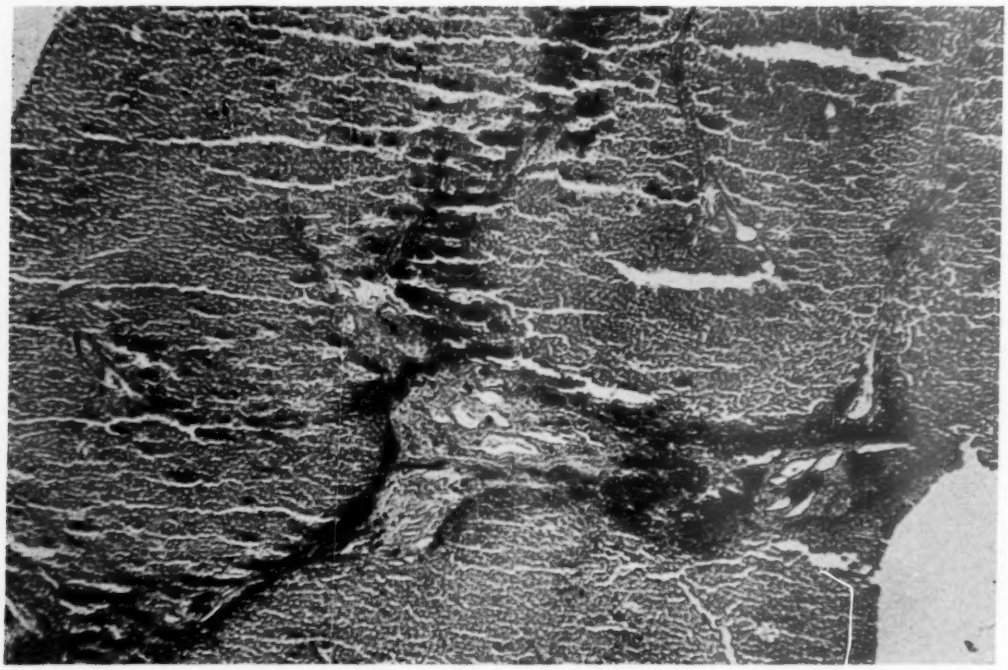

Fig. 6.—Photomicrograph (hematoxylin and eosin stain ×32) taken from the liver of dog B103 nine months after vena cava occlusion and four months after ligation of the hepatic and splenic arteries. There is hemorrhagic congestion and mild fibrosis with partial regeneration of liver parenchyma.

DISCUSSION

From these experiments it may be assumed that ascites produced by a Polythene band around the inferior vena cava may be modified by diet. These results have also been obtained by McKee and co-workers.[1] However, the amount of decrease was greater in dogs treated by ligation of the arterial supply to the liver and spleen than by dietary control. What is even more important the animals could be left on stock rations and the ascites did not increase in amount. If the animals with ligated hepatic and splenic arteries were put on a high-sodium diet their ascites increased slowly. This was ameliorated slightly when they were put on a high protein diet with only 0.5 Gm. of sodium per day intake. It is understandable that the ascites should increase with a high-sodium diet and decrease with a high-protein, low-sodium diet. The decrease in the formation of ascitic fluid resulting from ligation of the hepatic and splenic arteries is not entirely clear.

In previous discussions[8] one of us (J. K. B.) averred that the formation of ascites is probably the result of a combination of causes, namely: an increase in the hydrostatic pressure within the portal vein with dilatation of its branches and transudation of plasma, stagnant anoxemia increasing portal permeability with the production of an exudate rather than a transudate, hypoproteinemia due to insufficient ingestion or to the loss of protein in the ascitic fluid with decrease in osmotic pressure, and lymphorrhea caused by the increase in amount of lymph from the liver as described by Grindlay and his associates.[9]

A great increase in hepatic lymph flow occurs following chronic obstruction of the inferior vena cava above the liver with cellophane bands. The liver lymphatics become greatly dilated and enlarged but the lymphatics of the spleen and mesentery are not engorged. Although cirrhosis of the atrophic variety is not comparable to the type of cirrhosis produced by the occlusion of the inferior vena cava, it is possible that Grindlay's hypothesis concerning the formation of ascitic fluid may be important in its production in the human being. If this assumption is correct, ligation of the hepatic artery in decreasing intrahepatic portal venous stasis also decreases the volume of lymph flow which must be forced back into the systemic venous circulation thereby decreasing the amount of ascitic fluid. Certainly the liver is an important source of ascitic fluid and its formation is not caused entirely by a disturbance of hydrostatic and osmotic pressures, as shown by portal occlusion proximal to the liver and variations in osmotic pressures by plasmapheresis and diet-induced hypoproteinemia. Perhaps other methods of producing experimental cirrhosis will throw additional light on this problem. In this connection the recent work of Hahn and associates[10] seems to show that cirrhosis comparable to human portal cirrhosis may be produced in dogs by using radioactive colloidal gold.

CLINICAL APPLICATIONS

This discussion is limited to the experimental production of ascites by occlusion of the inferior vena cava and would be applicable to ascites due to cardiovascular, hepatic, and nutritional causes but not renal, inflammatory, or neoplastic causes. If the increase in portal pressure is a factor, its reduction by ligation of the hepatic and splenic arteries, as previously described, should be followed by decreased portal permeability due to lessened dilatation, and if portal flow is increased this should relieve the stagnant anoxemia and also reduce the lymphorrhea. Dietary control plays a significant role also as shown by the fact that a high-sodium diet increased the quantity of ascitic fluid and a high-protein, low-sodium diet diminished it.

These effects have been observed in man in the treatment of portal cirrhosis of the liver with ascites and have been confirmed by studies on twelve patients.[11] Three of the group continued to form ascitic fluid shortly after surgery when permitted an unrestricted diet high in sodium. A decrease in the amount of ascites and peripheral edema occurred when the diet was low in sodium and high in protein. This is due in part to the great amount of salt ingested by most cirrhotic patients, but, more important, by the retention of

sodium due to "cirrhotic nephrosis" which seems to prevent the loss of this cation by the renal tubules. The limits, however, are greatly extended by ligation of the hepatic and splenic arteries due partially to improvement in kidney function. Moreover, if sodium is removed through the gastrointestinal tract by cation-anion resins, patients may use more salt in their food. This encourages them to eat more protein which is very important; ultimately, no sodium restrictions are necessary. Some of our patients with advanced portal cirrhosis who had hepatic, splenic, and left gastric arterial ligations are now on regular diets without salt restriction and excreting normal amounts in the urine. However, one patient with passive hyperemic cirrhosis due to cardiac decompensation continued to form ascites in spite of ligations, dietary measures, and cation-anion resins.

The formation of ascites is really a plasmapheresis which occurs within the abdominal cavity, and the more fluid that is formed the greater the degree of hypoproteinemia. Therefore, it is desirable to limit the amount of loss and at the same time increase the amount of protein ingested. Paracentesis is usually followed by a greater amount of ascites due in part to changes in osmotic and hydrostatic pressures. With fluid surrounding the portal branches the hydrostatic pressure differential is not as great. Following paracentesis, as is well known clinically and experimentally, the effective portal hydrostatic pressure rises with increased transudation and more protein loss. Therefore, paracentesis should be done more often with removal of small quantities at a time. If the volume of fluid can be kept at a low level it will be tolerated and gradually it will improve after vascular and dietary control.

CONCLUSIONS

1. Ascites has been produced in the experimental animal by incomplete ligation of the inferior vena cava above the diaphragm with a Polythene band.

2. Studies of the amount and character of fluid, collateral circulation, portal pressures, liver function, and liver morphology have been described.

3. The treatment of experimental ascites is based upon dietary and pressure moiety control.

4. Our experiments indicate that this combination is definitely superior to either method alone.

5. Patients with advanced portal cirrhosis and ascites treated by hepatic, splenic, and left gastric arterial ligations are less likely to produce ascitic fluid in the immediate postoperative period when kept on a low-sodium (1.5 Gm. per day) and high-protein diet.

6. Passive hyperemic cirrhosis due to cardiac inadequacy may be accompanied by the production of small amounts of ascites after ligations, dietary control, and cation-anion resins. It is best treated by removing small amounts at frequent intervals rather than a large quantity at any one time.

Acknowledgment.—Many helpful suggestions were made by the Lilly Research staff.

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THE CONSTRUCTION OF FRESH AUTOGENOUS ARTERIAL GRAFTS

I. Use of the Splenic Artery to Bridge a Gap in the Aorta

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ON JAN. 28, 1947, an experimental program was launched in the Surgical Research Laboratory of the Children's Medical Center in Boston which led directly to the first successful use of preserved homologous arterial grafts[1] in human beings by Dr. Robert E. Gross. In the comparatively short space of time that has elapsed since this reinvestigation of the initial work of Carrel and others[2] was instituted, a prodigious amount of effort has been expended in various research centers to solve the many problems that have been raised.

Fresh autogenous venous grafts have satisfied the requirements for bridging gaps in small and medium-sized arteries[3] and for constructing shunts in the surgical relief of portal hypertension[4-6] and superior vena caval obstruction[7] as well as from the aorta to the coronary sinus.[8] Although segments of fresh autogenous inferior vena cava[9-12] and of preserved venous homografts[13] have been employed successfully to bridge gaps in the aorta of the experimental animal, use of this vessel in human beings has not met with enthusiasm. The inaccessibility of the inferior vena cava from the thorax and the high incidence of untoward sequelae following caval ligation[14] have been limiting factors in autotransplants. Rupture of a vein graft in the surgical treatment of an abdominal aneurysm has already been reported,[15] and Johnson and co-workers demonstrated an aneurysmal bulge in an experimental vein graft to the aorta.[10]

Preserved homografts of aorta and large arteries have supplied the most satisfactory solution to date for the problem of bridging a gap in the aorta in human beings. Blood vessel banks have been established in Boston,[16] New York,[17] Denver,[18] and other centers. The major difficulty in maintaining these banks, with the exception of front line military hospitals,[19] has been an inadequate supply of acceptable donor material.

There have been two main lines of investigation to remedy this situation. One of these has been concerned with improved techniques of preservation, so that the safe period of storage of grafts before they must be discarded might be prolonged. These have included refrigeration (Hufnagel,[20, 21] Deterling and associates[22]) and fixation by formalin (Peirce and co-workers[23]), glycerin,[24] and alcohol[25] among others. The second, the possibility of augmenting the supply by sterilization of contaminated grafts by high-voltage cathode ray irradiation, is being explored in the laboratory of Dr. Gross (with human application already accomplished[26]) and by Hui and co-workers.[27]

Functional success, with patent grafts, has thus been achieved with fresh and preserved, venous and arterial, autogenous and homogenous (as well as heterogenous[28]) transplants. The disturbing fact, however, has been that, with

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the exception of the fresh autogenous arterial graft, the cellular constituents of the transplants disintegrate, the muscle cells of the media disappear, and fibrous tissue replacement occurs, often with collagenous degeneration and calcification. Gross[29] has analyzed nineteen cases of coarctation of the aorta in which the narrowed segment had been replaced by a preserved homologous graft. In one patient calcification in the graft has been noted roentgenographically, and in another there is presumptive evidence of thrombosis. While some of the techniques of preservation are conducive to more severe changes than others, in none does the graft present a normal or healthy histologic appearance. Miller and associates[30] have confirmed the previous observations that only in the fresh autogenous graft may one anticipate preservation of the histologic integrity of the media.

The general acceptance at this time of the preserved arterial homograft represents a compromise, with a transplant that might be intact both functionally and anatomically as the ideal. The hope that survival of the cells of a homograft might be enhanced by the adrenocorticotropic preparations has been short-lived. To date, no adequate source of autogenous arterial tissue for fresh aortic grafts has been devised. Recognition of the importance of developing a source of fresh autogenous arterial tissue from which grafts of large diameter might be constructed led to a consideration of the possible use of the splenic artery for this purpose. A long artery of moderate size, associated with an organ that may be sacrificed without jeopardizing the welfare of the subject, supplies the basis for these experiments.

EXPERIMENTAL METHOD

Large mongrel dogs, averaging 50 pounds in weight, were anesthetized with intravenous veterinarian Nembutal. The peritoneal cavity was entered through a liberal left paramedian muscle-splitting incision. The spleen was mobilized and all of its attachments divided, to the pedicle. The tail and body of the pancreas were dissected from the splenic artery, and the artery ligated at as high a level as possible. This usually resulted in a length of available splenic artery measuring from 6 to 10 cm. between the proximal ligature and the hilus of the spleen where the artery breaks up into branches. Autotransfusion with splenic blood was effected by squeezing the spleen, following which the vein was ligated and the spleen resected, with a long pedicle.

At a separate table, the splenic artery was isolated from the vein, and the remainder of the tissue discarded. The artery was split longitudinally, an attempt being made to include any branches in the line of the incision. The opened artery was divided transversely into 3 (or 4) equal segments. The panels thus created were then fashioned into the tubular graft by the steps illustrated in Fig. 1. Each longitudinal suture line consisted of a continuous over-and-over stitch of No. 00000 Deknatel silk, to which petrolatum had been applied, on a small straight atraumatic needle. The saline drip to prevent drying of the tissue was of great importance.

The lower portion of the abdominal aorta was mobilized, usually with division of 1 or 2 pairs of lumbar branches. The aorta was occluded by, and divided between, 2 multitoothed clamps of the Potts type, with resection of a segment up to 1 cm. in length. This gap was bridged by the tubular graft just constructed. The graft was anchored into place at each end. Each circumferential suture line consisted of a continuous everting mattress suture of No. 00000

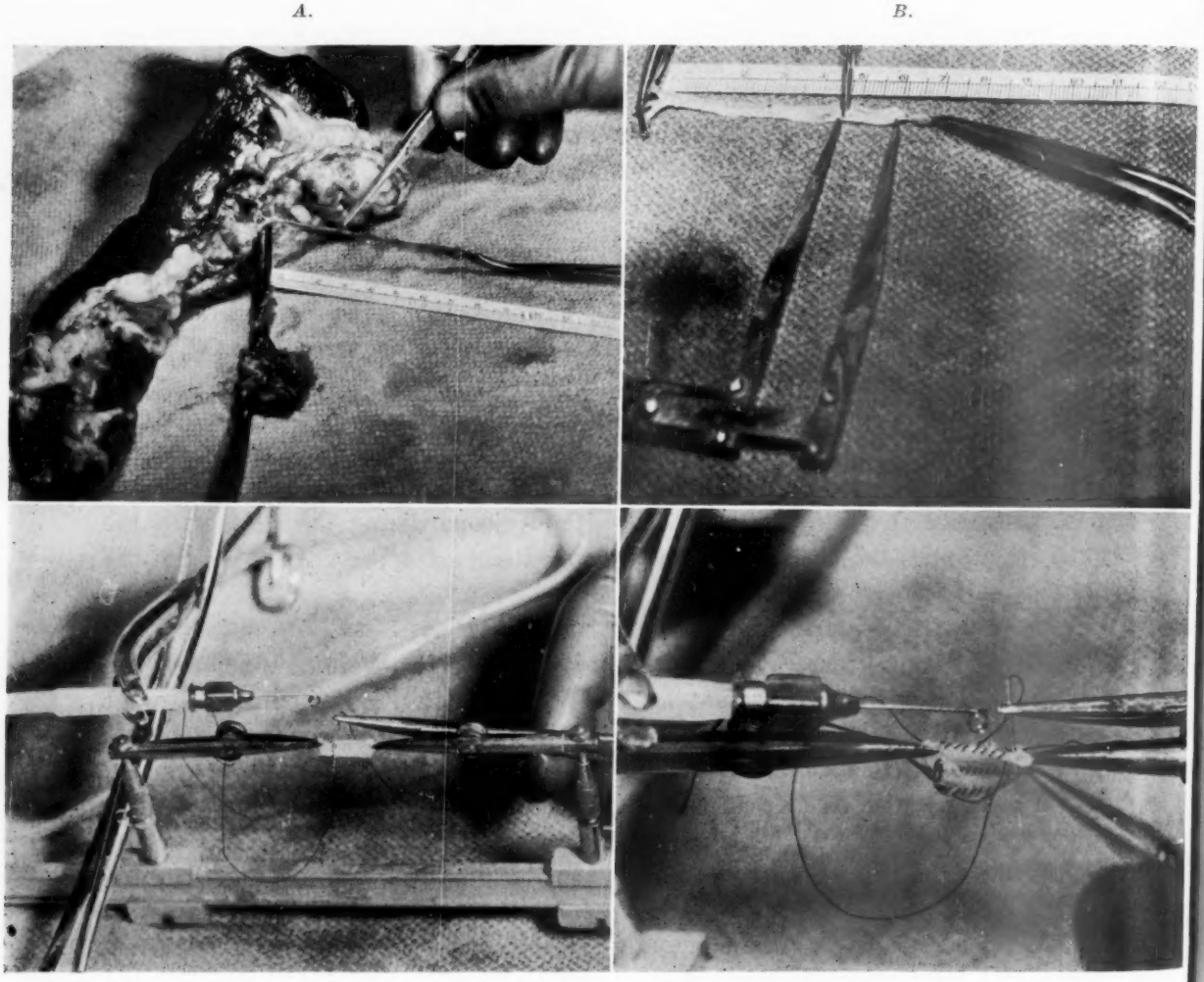


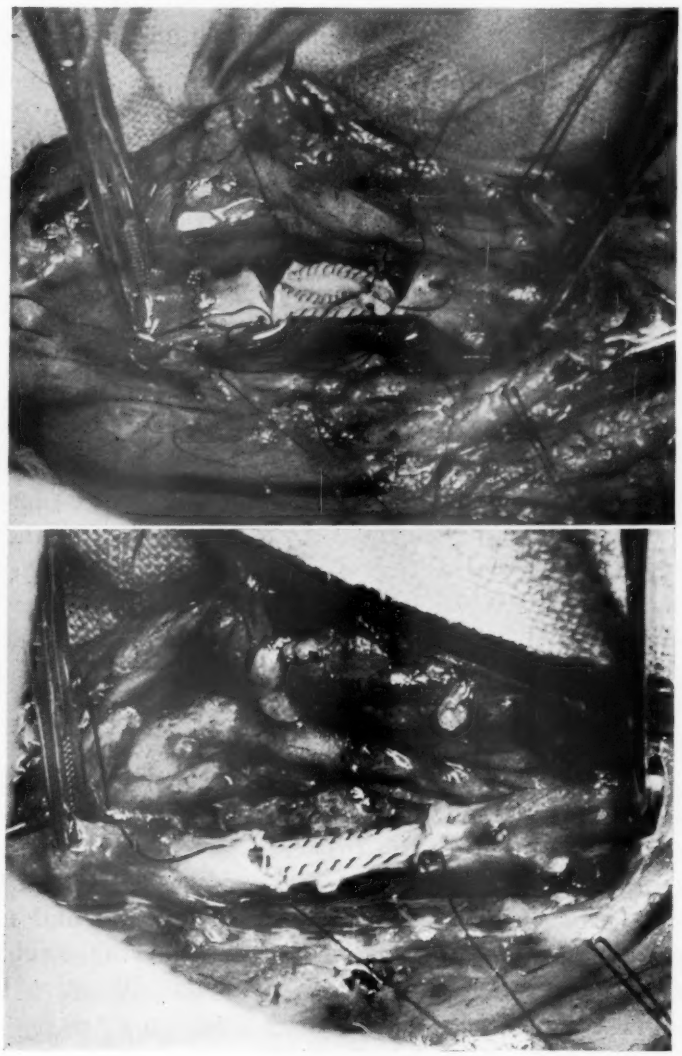
Fig. 1.—Fabrication of tubular graft: *A*, 7 cm. length of splenic artery isolated from hilus and vein; *B*, artery split in long axis, being divided transversely into equal panels; *C*, suture line commenced with first 2 panels; *D*, tubular graft almost completed.

Deknatel silk on a small round atraumatic needle. Care was taken to straddle the end of each longitudinal suture as it was reached. Following completion of the anastomosis, the transplant was irrigated with saline solution introduced by a needle into the aorta, and tested for leaks. Large leaks were repaired by interrupted sutures. The graft was wrapped in compressed Gelfoam,* size 100,

*Supplied through the generosity of The Upjohn Company, Kalamazoo, Mich.

and the distal occluding clamp released, followed by gradual release of the proximal clamp while the graft was gently compressed for several minutes. The Gelfoam usually became bloodstained quickly. When active bleeding had been eliminated, metal dura clips were placed as markers for roentgenographic identification, the posterior parietal peritoneum was united over the graft, and the

A.



B.

Fig. 2.—Fabricated tubular graft sutured into gap in abdominal aorta: *A*, graft anchored to each end of aorta; *B*, second circumferential anastomosis almost complete.

peritoneal cavity was closed in layers. No anticoagulants were used, either locally or systemically. Each dog received an infusion of 1,000 c.c. of 5 per cent glucose in water intravenously during the operation, and 300,000 units of penicillin per day for the first 3 postoperative days (Fig. 2).

After the technique had been acquired, splenectomy and construction of the graft consumed about one hour. By mounting the artery panels in the jig contrived by one of us (A. K.), it was possible for one man to carry out the entire fabrication of the graft alone. While he was thus occupied, the rest of the team mobilized the lower abdominal aorta, from below the renal arteries almost to the aortic trifurcation.

EXPERIMENTAL RESULTS

A total of 30 dogs was utilized for these observations. Technical pitfalls accounted for many early failures. An analysis of the experiments in 3 consecutive groups of 10 each emphasizes the importance of evolving a definitive technique. In the first group of 10 there were 4 good grafts, with only 2 long-term survivors; of the second 10, 6 grafts were satisfactory and 4 dogs did well; in the final 10 there were 8 good grafts with 6 survivors. The discrepancy between the 18 good grafts and 12 long-term survivors is accounted for by 6 postoperative deaths due equally to distemper, aspiration pneumonia, and anesthesia.

Many of the early failures were attributable to necrosis in the graft due to excessive pressure by the jig holders; the placing of the sutures in the fabrication of the graft in such a way that too much or too little tissue was included, or strands of adventitia inadvertently carried along; drying of the panels; improper construction of the anastomotic suture lines; and the lack of Gelfoam. The completed technique included careful adjustment of the jig holders, meticulous placing of all sutures, a continuous saline drip to keep the panels moist during fabrication of the graft, and a backing for the graft of compressed Gelfoam. By observing all of these details, there was only 1 unsatisfactory experiment in the last 8 consecutive dogs, and that was due to clumsiness on the part of the operator in performing the anastomosis.

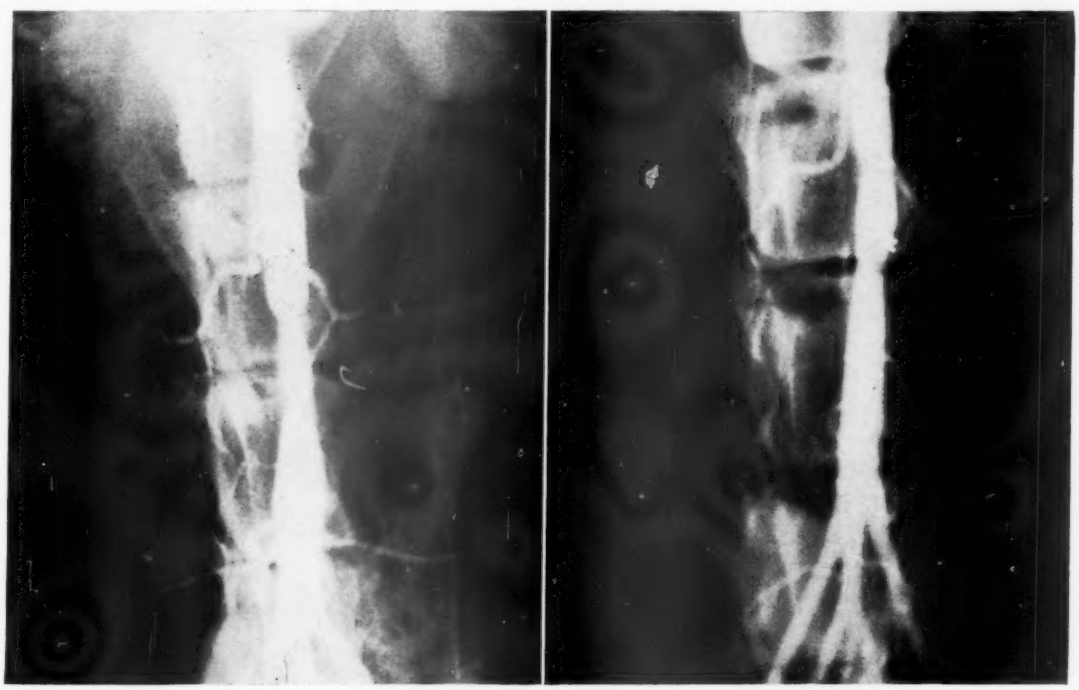
The average diameter of the pulsating abdominal aorta measured 11 mm., and that of the splenic artery 3 mm. The 3 panel grafts employed in the early experiments were uniformly smaller in caliber than the aorta, but the 4 panel grafts employed later made a nice fit. There was usually a sufficient length of splenic artery available to permit construction of a tubular graft up to 2 cm. long. In only 1 instance was the splenic artery so thin and narrow that a satisfactory graft was not created. Pancreatitis following mobilization of the splenic artery occurred only once, with acute gastric dilatation leading to the death of the animal.

Hemorrhage from rupture of the graft occurred 6 times in the first 14 experiments, and this was eliminated as the technique became standardized. There were 4 instances of thrombosis of the graft, of which 1 was associated with infection and the other 3 with the traumatic causes already discussed.

Use of the splenic artery in 30 dogs thus resulted in 18 satisfactory aortic grafts. Of the 12 failures, 11 were due to avoidable factors that were eliminated as the experiments progressed, and in only 1 dog was the artery itself unsuitable for the fabrication of a tubular graft.

Functional evaluation of the grafts has been based upon the postoperative course and upon aortography. Retrograde aortagrams were made soon after operation and before sacrifice on every animal. In no case had the caliber of the graft lessened in the interval between examinations, the longest-term survivor to be sacrificed to date having survived 6 months. Aortography was done by injecting 30 c.c. of 35 per cent Diodrast rapidly in retrograde fashion into a cannulated femoral artery and taking rapid films with the Fairchild 9½ by 9½ inch magazine roll camera (Fig. 3).

Anatomical evaluation of the transplants was based on gross and histologic observations. In all the specimens examined within 4 months after operation, there was a distinct difference between the color of the intima of the graft and



A. *B.*

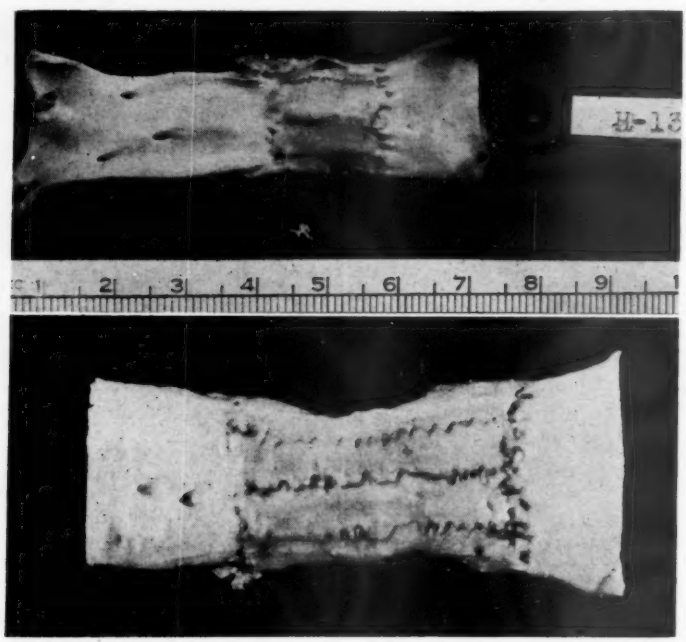
Fig. 3.—Retrograde aortagrams 2 weeks after insertion of *A*, 3 panel, and *B*, 4 panel arterial autografts.

that of the host aorta. A tan in the early specimens was gradually replaced by a pearly gray in the older ones, so that by 6 months after operation the color of the intima was uniform. In dogs dying within the first 10 days after operation the intimal surface was shaggy, and the sutures bare. Small flat mural thrombi were not uncommon, more often attached to the graft panels than to the sutures. The importance of the speed and force of blood flow in the aorta in minimizing thrombus formation cannot be overemphasized. By the tenth postoperative day the circumferential sutures and the ends of the longitudinal sutures were partly covered by endothelium in 2 specimens, with bare areas in the central portions of the longitudinal sutures and a few tiny shallow ulcerations in the panels. Two additional specimens examined on the fifteenth and

sixteenth days, respectively, showed almost complete smooth covering of the sutures, with small shaggy patches in the central part of the graft. Studies have been conducted on 5 grafts examined at 2, 3, 4 (2 dogs) and 6 months after insertion. No thrombi or ulcerations were present, and the intimal surface of the transplants, including the suture lines, was completely covered by endothelium. Straightening of parts of the longitudinal suture lines in the six-month specimen indicates that some of the loops have pulled out of the panels in these areas; the silk is still covered by endothelium (Fig. 4). Additional dogs are being maintained for long-term survival observations.

The thickness of the graft, which at the time of insertion was considerably less than that of the aorta, gradually increased with the organization of the Gelfoam, passing through a stage of excessive thickness to a final state in which the walls of host and graft had approximately equal measurement.

A.



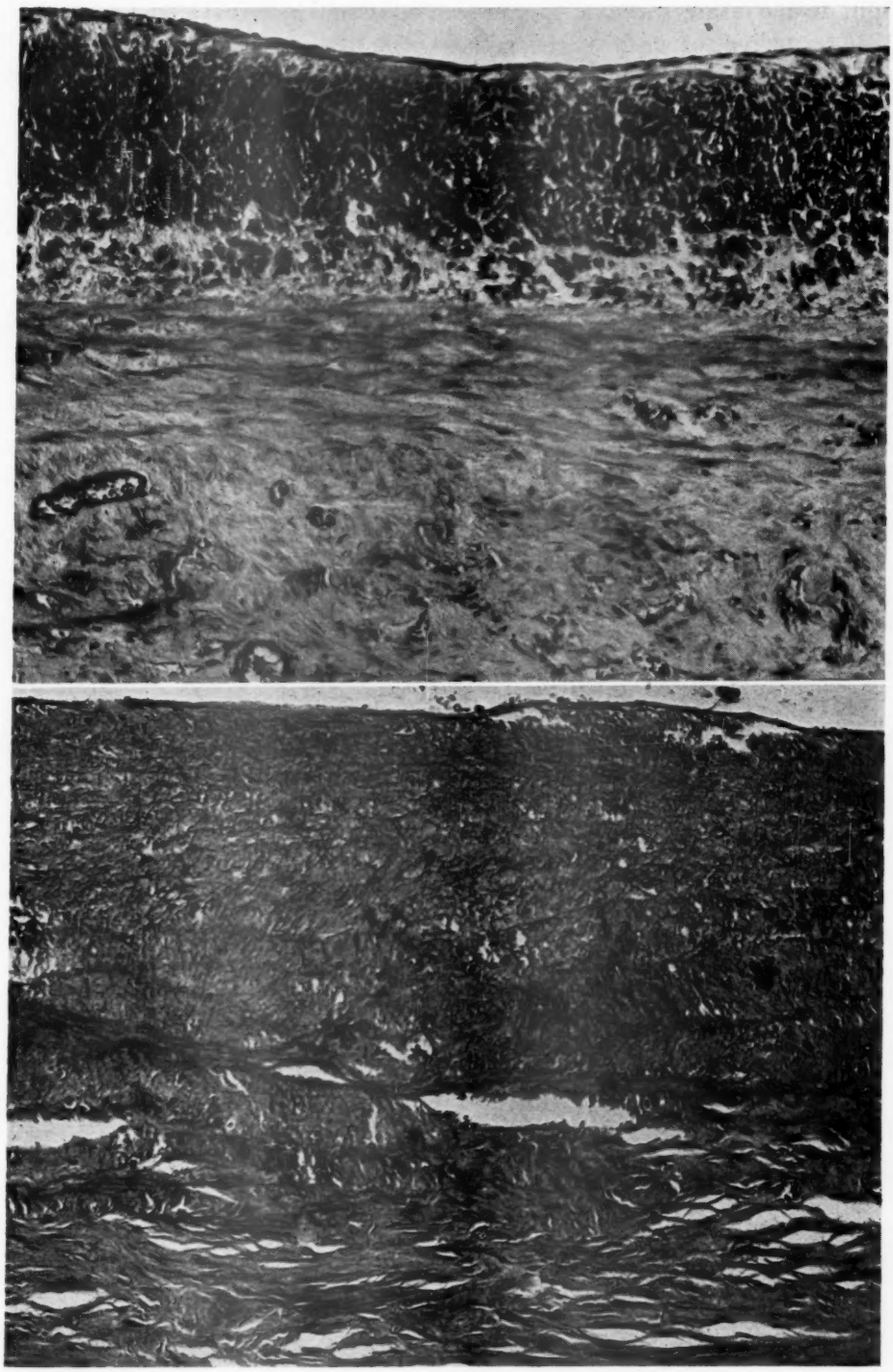
B.

Fig. 4.—Gross appearance of fabricated tubular grafts *A*, 65, and *B*, 195 days after implantation. Suture lines are smoothly covered by endothelium, and partly pulled straight in *B*.

The histologic appearance of these grafts constitutes the crux of the entire study. The very thin intimal layer of the original splenic artery was replaced by a fine endothelial covering resting on a fairly dense layer of connective tissue. The subendothelial fibrosis varied markedly from 1 specimen to another, and in different parts of the same specimen; it may represent, in part, organization of blood clot. The anastomotic junction was occupied by a wedge of fibrous tissue with a thin overlying endothelial layer.

Preservation of the integrity of the media was the most striking characteristic of the grafts. In animals sacrificed at 2 months, 4 months, and at 6

A.

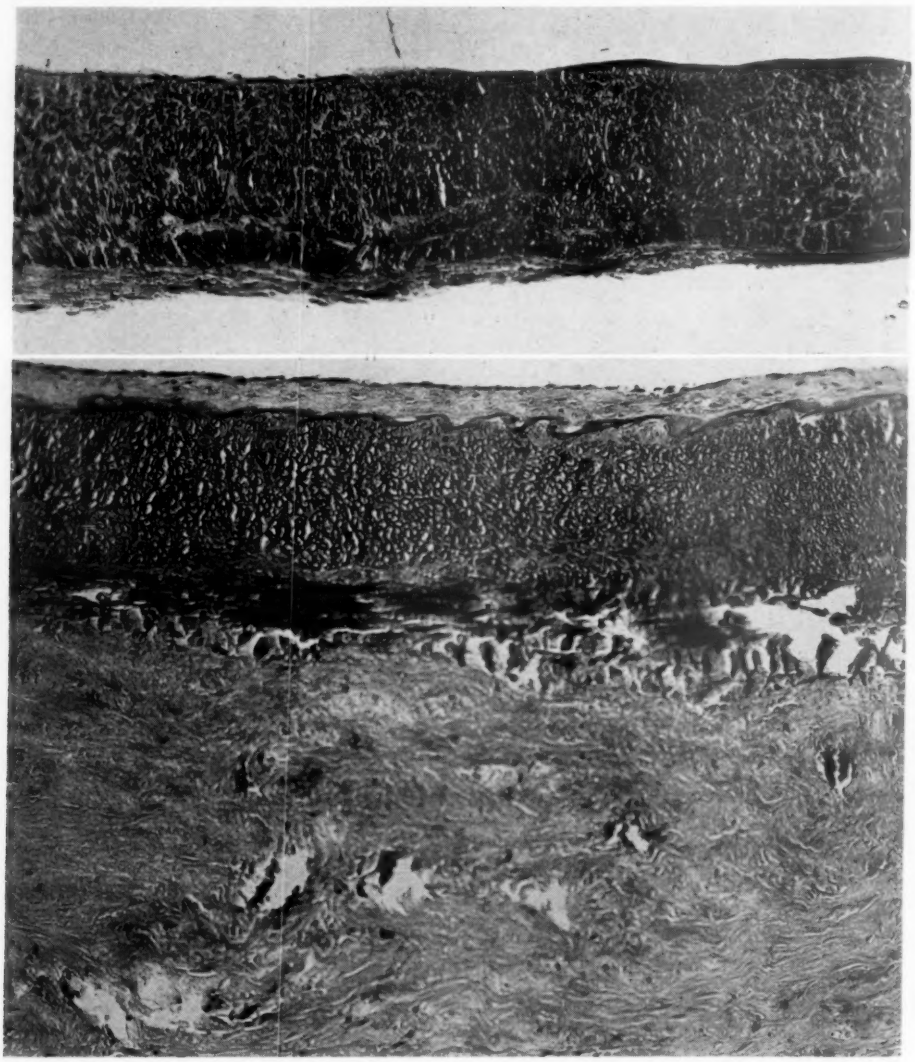


B.

Fig. 5.—*A*, Survival of media of fresh arterial autograft, postoperative 137 days. *B*, Collagenous degeneration of media of fresh aortic homograft, postoperative 83 days. (Masson stain, original ×180.)

months the thickness of the media was the same as in the original splenic artery. A slight to moderate increase in connective tissue was revealed by the Masson stain, but survival of most of the muscle cells of the media was the rule. This is in direct contrast to the fate of the media in homografts, where collagenous

A.



B.

Fig. 6.—*A*, Normal splenic artery, and *B*, splenic artery—aortic graft 195 days after insertion. Note subendothelial fibrosis, survival of media, and extensive thickening of adventitia (organized Gelfoam). (Masson stain, original ×180.)

degeneration and connective tissue replacement occur uniformly. Fibrillation and thinning of the elastic tissue laminae were also less in the autografts than in the homografts (Fig. 5).

In 2 dogs, sacrificed 3 and 4 months postoperatively, it was noted that the integrity of the media was distorted to a far greater degree than in the other

specimens. The thickness of the media was considerably diminished, and there was a substantial reduction in the number of surviving muscle cells. In these specimens also the intimal layer was much thicker than in the others, suggesting a more intense reaction, possibly traumatic. Compromised survival of the media in these specimens may have been on the basis of compression between thick intimal and dense adventitial layers. This suggestion receives support from study of adjacent areas in a 3 month transplant: the media is intact beneath a thin intima, and markedly changed in the region of a thick intima. Nourishment of the innermost layers of the media by oxygenated blood in the lumen of the vessel is also indicated by a comparison of these two zones, in which the adventitia is of uniform thickness and the appearance of the media is correlated with changes in the intima.

A remarkable transformation of the thin adventitia of the graft to a thick dense layer of connective tissue accompanied the organization of the Gelfoam. This was in progress in a 2 month specimen, and complete at 3 months. The newly formed outer wall was liberally supplied with blood vessels in all of the specimens (Fig. 6).

The homologous transplants utilized for comparison with this group of fabricated autografts were obtained from a series of aortic grafts carried out by one of us (E. S. H.) with Dr. Robert E. Gross in the surgical research laboratory of the Children's Hospital, Boston, in 1947. Resection of a segment of the abdominal aorta in dogs was performed under the same conditions as in the present experiments. The gap was bridged by a fresh segment of aorta taken from donor dogs in 10 animals, with 2 deaths. Transplantation of aortic segments preserved for 6 hours in Ringer's solution at ordinary icebox temperatures was performed 9 times, with 2 deaths. The technique of anastomosis was constant in all the operations. The dogs were sacrificed after periods ranging from 2 months to 1 year postoperatively; in each series there were 5 grafts classified as good to excellent. The degeneration of the media and replacement by fibrous tissue in these specimens conform to the biologic behavior pattern described by others for fresh and preserved homotransplants.[2, 10, 11, 31-34]

DISCUSSION

At the third annual meeting of the Society for Vascular Surgery in Atlantic City on June 5, 1949, Dr. Julian Johnson and his co-workers[9] presented the use of autogenous femoral vein grafts to construct shunts in 2 patients with cyanotic heart disease. In the discussion which followed this paper it was stated by Dr. Gross, and generally agreed, that the repair of blood vessel defects should be accomplished by direct end-to-end approximation of the vessel, by a fresh autogenous graft, or by a preserved homograft, in that order of preference. The lack of availability of arterial tissue has prevented the use of fresh autogenous arterial grafts for bridging gaps in the aorta. This was reemphasized by various discussants at the seventy-first annual meeting of the American Surgical Association in April, 1951.[12]

If the histologic integrity of the media of a graft is of importance—and it is difficult to think that it would be unimportant—this demonstration of the

feasibility of constructing autogenous arterial grafts may have potential clinical application. In a series of observations based on 17 autopsies on adult human beings in the Pathology Laboratory of the Montefiore Hospital,* the circumference of the splenic artery measured 1 to 1.5 cm. in 68 per cent of the examinations, the circumference of the thoracic aorta measured 5 to 7 cm. in 71 per cent, and that of the abdominal aorta 4 to 5 cm. meters in 60 per cent. Approximately 10 to 12 cm. of splenic artery were estimated as being surgically accessible. These relative measurements are comparable to those in the dog, and indicate the suitability of this tissue for aortic grafts. The splenic artery is accessible from either the abdomen or the left side of the chest.

The observations made in these experiments would tend to confirm the concept that the intimal surface of the graft is replaced by cellular elements from the host, and that the ingrowth of endothelium commences from the host at each end of the graft. This seems more likely than the formation of endothelium from the organization of blood clot in situ as suggested by Wylie and associates.[35] Support is also lent to the impression of Sako and co-workers[36] that the longitudinal suture lines may act as struts along which the growth of endothelium may be accelerated. These authors transplanted tubular grafts, constructed from pericardium and from fascia, between the divided ends of the thoracic aorta in dogs. Thickening and dilatation of the transplants occurred, with the deposition of atheromatous material.

The density of the newly formed adventitia, resulting from organization of the Gelfoam, compared favorably with that described by Wylie[35] following the use of fascia lata as a support around weakened arteries. The importance of the adventitia in terms of the bursting strength of an artery has been documented by Winternitz and co-workers.[37] Organization of the Gelfoam in these experiments suggests the usefulness of this material in reinforcing vascular suture lines, transplants, and blood vessels that have been subjected to surgery. This behavior of Gelfoam contrasts with the persistence of the substance in the intracranial cavity, where it has been found almost unchanged as long as 2 years after insertion.[38]

The growth of anastomotic suture lines[39] and of fresh autogenous aortic and vena caval grafts has been demonstrated.[10, 11] Growth of the fabricated autograft is under investigation. It is not suggested that the splenic artery affords the only or the best source of tissue for a fabricated autogenous arterial graft. Excessive tortuosity and advanced atherosclerosis may eliminate this vessel at times. Other sources of arterial tissue merit consideration.

SUMMARY

1. A technique has been devised for the fabrication of fresh autogenous arterial transplants from segments of the splenic artery.

2. Tubular grafts may be fashioned to any required diameter.

3. Grafts constructed from segments of the splenic artery have been used to bridge a gap in the abdominal aorta in a series of dogs.

*By Dr. Stanley Altman.

4. An adequate functional result has been obtained, with long-term patency of the grafts and survival of the animals.

5. Preliminary histologic observations, in survival studies up to 6 months postoperatively, indicate preservation of the integrity and survival of the muscle cells in the media of the grafts.

6. These fresh autogenous arterial grafts are functionally equal to, and anatomically superior to, aortic homografts.

7. The disadvantages of splenectomy and the time required to construct the graft are offset in part by eliminating the problems of supply, sterilization, preservation, and the biologic specificity of tissue proteins.

8. Fresh autogenous vein grafts are ideal for bridging gaps in arteries of small to moderate size. The use of fabricated fresh autogenous arterial grafts is recommended for defects involving the aorta.

We are grateful to Dr. Harry Zimmerman, Chief of the Laboratory Division of the Montefiore Hospital, for his guidance in interpreting the histologic preparations, and to Dr. Joel Schwartzman of the Department of Roentgenology for his help in aortography.

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THE PRODUCTION OF CHRONIC GASTRIC HYPERVAGOTONIA

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THE concept of the causal interrelationship of ulcerative gastric lesions and neurological lesions has been under discussion for over 100 years[1-3] and antedated the definitive studies of Pavlov and Shumov-Simanovsky[4] on gastric innervation by about 80 years. These early suppositions were based on two facts: (1) at autopsy there is frequently coincidence of central nervous system lesions and ulcerative lesions of the stomach, (2) the vagus nerve is the only obvious pathway from brain to stomach. After the work of Pavlov and Shumov-Simanovsky,[4] which assigned to the vagus nerve its essential role in gastric function, the neurogenic theory of peptic ulcer etiology increased in popularity. The work of von Bergmann,[5] Dragstedt,[6] Cushing,[7] Strassmann[8] and many others has added evidence for the neurogenic theory. This indirect evidence largely consists of the following: (a) the vagus nerve has known secretory and motor functions in the stomach, (b) hypersecretion and hypermotility frequently accompany peptic ulceration, (c) brain lesions and gastric ulceration sometimes coexist, (d) the vagi and the highest centers are connected, (e) vagotomy or parasympatholytic drugs can alleviate or cure peptic ulcer. Thus there is a large body of indirect evidence associating the vagus nerve with ulcer etiology. Apparently, however, there is no direct evidence of causal relationship. Peptic ulceration has never been directly demonstrated to result from hypervagotonia nor has an experimental condition of truly prolonged hyperactivity of the vagus nerve been successfully accomplished. Many attempts have been made (Stahnke,[9] Vineberg,[10] and others) but all of these have been limited to intermittent periods of a few hours of electrical stimulation and have thrown little light on the role of the vagi in peptic ulceration.

We decided therefore to make a further attempt to accomplish prolonged hyperfunction of the gastric vagi. Two methods were employed for this purpose: (1) permanent indwelling electrodes were applied to the vagus nerve and, after postoperative recovery, continuous electrical stimulation was applied, and (2) anastomosis of the phrenic and vagus nerves in the thorax was done in the hope that phrenic respiratory impulses would traverse the distal vagus. This study was begun almost three years ago when no record of phrenicovagus anastomosis could be found in the literature. Since that time, however, such reports have appeared (Ivy, Grossman, and Bachrach[11] and Jefferson, Phillips, and Necheles[12]). In both of these investigations unsuccessful attempts were made to induce peptic ulceration. Neither report included complete gastric function studies and both concluded that effective functional anastomosis had not occurred and might not be feasible.

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METHODS

Surgical.—Five adult mongrel male dogs were used. Each animal was provided with either a modified Thomas gastric pouch[13] or a metal cannula gastrostomy. Intravenous sodium pentobarbital anesthesia was routinely used and positive pressure artificial respiration by endotracheal tube was employed when the thorax was opened. The approach to the vagi was always via the left seventh intercostal space. In two of the dogs the right vagus nerve was dissected free between the root of the lung and the diaphragm and a small Lucite chamber bearing tantalum electrodes (Fig. 1) was applied to the nerve. Leads of tantalum wire insulated in polyethylene tubing were brought from the electrodes out through an intercostal stab wound. A 2 cm. segment was excised from the left vagus nerve, the stab wound closed tightly around the leads and the thorax closed in the usual way. In the remaining three animals the right vagus and left phrenic nerves were carefully isolated between the root of the lung and the diaphragm and both were sectioned with a sharp scalpel. The proximal cut

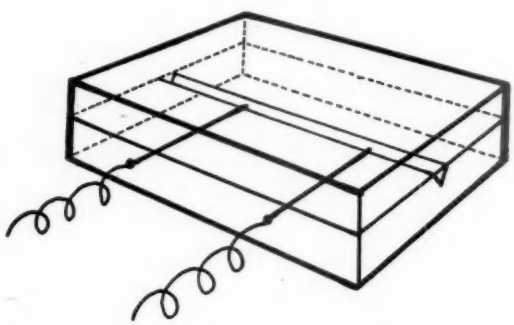

Fig. 1.—Lucite electrode chamber for chronic stimulation of the vagus nerve. The two halves are separated and the nerve laid in the V-groove in contact with the electrodes. The two halves of the chamber were held together with silk sutures.

end of the phrenic and the distal cut end of the vagus nerves were then carefully joined end to end with four or five sutures passed through the sheaths (Fig. 2). The nerves were handled with sponge-rubber-shod instruments and the suturing was done with fine silk and specially ground needles. A 2 cm. segment of the left vagus nerve was excised and the chest closed.

Postoperatively the animals received four daily doses of 200,000 units of acqueous procaine penicillin intramuscularly. There was no operative mortality or morbidity.

Types of Studies.—One of the animals with indwelling electrodes was equipped with a gastrostomy, the other with a gastric pouch. Two weeks after operation the animals were restrained in stalls and control collections made of the spontaneous fasting (18 hr.) gastric juice. The tantalum leads were then connected to a thyratron stimulator for continuous indefinite stimulation (1 Ma., 15 shocks per second). The gastric juice was collected continuously during stimulation.

The first animal with phrenicovagus anastomosis was permitted a four-month recovery period after which the thorax was opened under sodium pentobarbital anesthesia. Leads were taken off the vagus nerve distal to the anastomosis with the left phrenic nerve and off the intact right phrenic nerve in an attempt to demonstrate synchronous showers of action potentials. The second animal with phrenicovagus anastomosis expired of unrelated causes before studies could be started.

The third animal with the nerve anastomosis was studied before and after operation. This animal was provided with a gastrostomy. Preoperatively collections of fasting (18 hr.) gastric juice were made both without stimulation

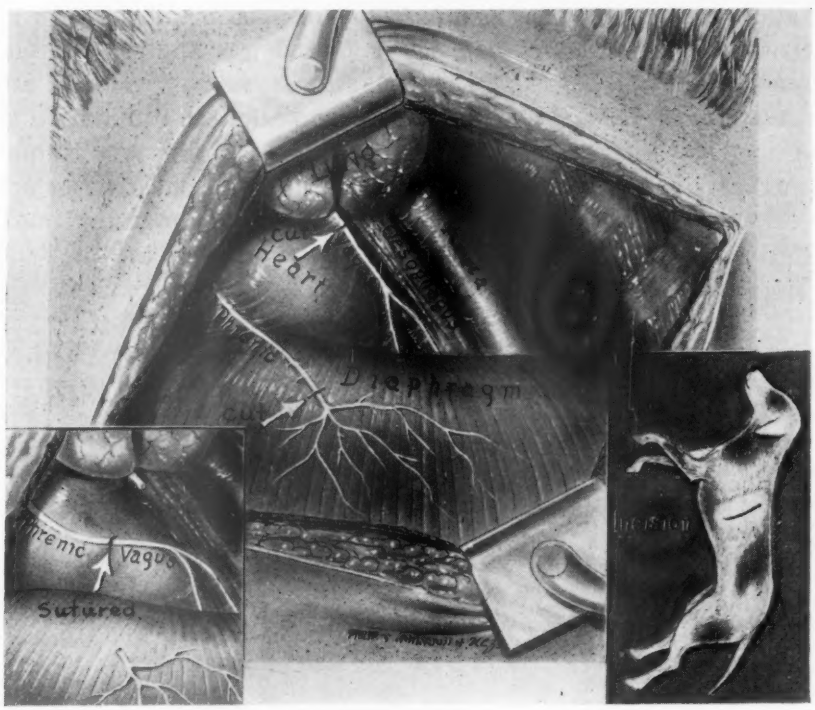

Fig. 2.—Detail of phrenicovagus anastomosis. The two arrows in the center drawing show points of transection of the phrenic and vagus nerves. Lower left cut shows anastomosis.

and during insulin stimulation. Similar collections were continued after a two-week postoperative recovery period, until the animal died of volvulus in the fifteenth week after operation. Gastric motility in this animal was observed by means of cinefluorography.[14] Attempts were made to influence gastric function by altering the phrenic discharge rate with elevated environmental temperatures and carbon dioxide inhalations.

Gastric Juice.—The glass electrode was used to measure pH. Aliquots of the gastric juice were titrated electrometrically with 0.1N NaOH to pH 3.5 for free acidity and to pH 8 for total acidity.

Peptic activity of aliquots of the gastric juice was determined by the method of Riggs and Stadie.[15]

Regular crystalline insulin was administered intravenously in a dosage of 0.5 unit per kilogram of body weight. Blood sugar determinations were made just before injection and 45, 90, and 150 minutes thereafter, using the method of Somogyi.[16]

Motility.—The fasted animal was given a thin suspension of barium sulfate by stomach tube and placed before a fluoroscopic screen. The image on the screen was then recorded in the form of a motion picture.

RESULTS

Electrical Stimulation by Way of Indwelling Electrodes.—

Dog 1 (gastrostomy): Unstimulated secretion from this animal in the fasting state consisted of a very small amount of alkaline mucus with very little peptic activity. Continuous electrical stimulation was applied and maintained for 26 hours, at the end of which time the animal escaped restraint and pulled out the intrathoracic leads. During the entire period of stimulation there was a marked increase in output of HCl and peptic activity (see Table I). At autopsy the vagus nerve was found to be essentially normal within the electrode chamber. The gastric mucosa was edematous, red, congested, and showed scattered petechial mucosal hemorrhages, particularly in the prepyloric area. Nothing suggesting peptic ulceration was found.

TABLE I. GASTRIC RESPONSES TO ELECTRICAL STIMULATION OF THE VAGUS NERVE

			MEAN HOURLY VALUES			
			HCl (IN mM)			
	NO. EXPTS.	pH	FREE	TOTAL	PEPSIN*	VOLUME (IN ML.)
Dog 1. Gastrostomy control values	5	6.5-7.9	0	0.18	0.74	–
Electric stimulation	1 (26 hrs.)	1.2	3.45	5.10	6.90	–
Dog 2. Gastric pouch control values	4	6.7-7.6	0	trace	.026	0.15
Electric stimulation	5	1.2-1.3	0.40	0.53	.79	4.6

*Expressed as "K" units (according to Riggs and Stadie[15]) times volume.

Dog 2 (gastric pouch): Unstimulated secretion from this animal in the fasted condition consisted of very scant amounts of alkaline mucus of very low peptic activity. Electrical stimulation induced a marked elevation in volume, acidity, and peptic activity (see Table I). It was found that electrical stimulation was effective for about five hours after which time the pouch secreted essentially basal amounts of juice. This stimulation was repeated daily but after the fifth day became ineffectual and was discontinued on the eighth day. At autopsy no abnormalities were grossly discernible in the stomach or intestine. The vagus nerve within the electrode chamber was essentially normal. Histologic examination yielded no additional information.

Phrenicovagus Anastomosis.—

Dog 3: Four months after operation leads were taken off the vagus nerve below the anastomosis and off the intact right phrenic nerve. The showers of

action potentials from both sources were synchronous, indicating that phrenic respiratory impulses were passing across the anastomosis into the distal vagus trunk. Microscopic examination of the anastomosis showed fibers from the proximal phrenic crossing the anastomosis into the distal vagus nerve. No gastrointestinal abnormalities were observed.

Dog 4: Dog 4 died of unrelated causes two weeks after the operation. At autopsy the anastomosis was grossly intact and apparently healing in good order.

Dog 5 (gastrostomy): Before operation unstimulated fasted gastric secretion was scant (Table II). Following insulin administration the blood sugar consistently fell to roughly 50 per cent of the normal fasting level in 90 minutes and returned to normal in about 150 minutes and there was a sharp rise in free and total acidity and peptic activity of the gastric juice. Following operation no secretory response to insulin was ever again elicited indicating that the connections between the vagal centers and the stomach were permanently interrupted. In the immediate postoperative period (2 to 4 weeks) there was a marked fall in volume, disappearance of free HCl, very small amounts of total HCl and very low peptic activity. There was no response to insulin although the usual blood sugar reduction occurred. In this period the motility studies showed a flaccid stomach which demonstrated no functional activity. The antrum was quiescent.

TABLE II. GASTRIC RESPONSES BEFORE AND AFTER VAGOTOMY AND PHRENICOVAGUS ANASTOMOSIS

DOG 5	NO. EXPTS.	pH	MEAN HOURLY VALUES		
			HCl (IN mM.) FREE	TOTAL	PEPSIN (IN K-UNITS)
Before Operation*					
Spontaneous secretion	4	6.4-7.5	0	0.20	0.71
Insulin stimulated	6	1.1-1.3	3.96	4.59	7.70
Immediately postoperative					
Spontaneous secretion	4	6.6-7.0	0	0.16	0.284
Insulin stimulated	3	6.5-6.8	0	0.24	0.292
12 to 14 weeks postoperative					
Spontaneous secretion	7	1.7-7.0	0.09	0.28	0.49
Insulin stimulated	4	1.6-6.8	0.16	0.37	0.38

*Double vagotomy plus anastomosis of the right vagus and left phrenic nerves.

Four and eight weeks after operation the situation remained unchanged. Between 12 and 14 weeks after the phrenicovagus anastomosis, changes in gastric secretory and motor behavior were apparent. The secretory behavior was quite inconsistent and the ranges of acid production and peptic activity were wide. However, free HCl returned in considerable amounts in some collections. There was increased total acidity and peptic activity. The maximum values obtained per hour were free HCl 0.442 mM., total HCl 0.731 mM., pepsin 0.46 unit. There was no response to insulin hypoglycemia. Response to increased respiratory rate induced by elevation of room temperature or by CO_2 inhalation was inconclusive. Moderate increases in respiratory rate gave secretory responses

in the upper range of normal; panting appeared to diminish secretion. During this period (12 to 14 weeks postoperatively) the motility studies showed the presence of waves traversing the antrum and increase in tonus of the whole organ (Fig. 3). No motor changes could be demonstrated to result from increasing the respiratory rate.

The animal died of a volvulus in the fifteenth week. Microscopic sections of the nerve anastomosis showed phrenic fibers traversing the anastomosis to the distal vagus nerve. No gastrointestinal pathology other than the volvulus was observed.

DISCUSSION

Two techniques for the creation of prolonged hypertonia of the subdiaphragmatic distribution of the vagus nerve have been attempted. In both preparations hypersecretion resulted and, in the case of the phrenicovagus anastomosis, motility changes were observed.

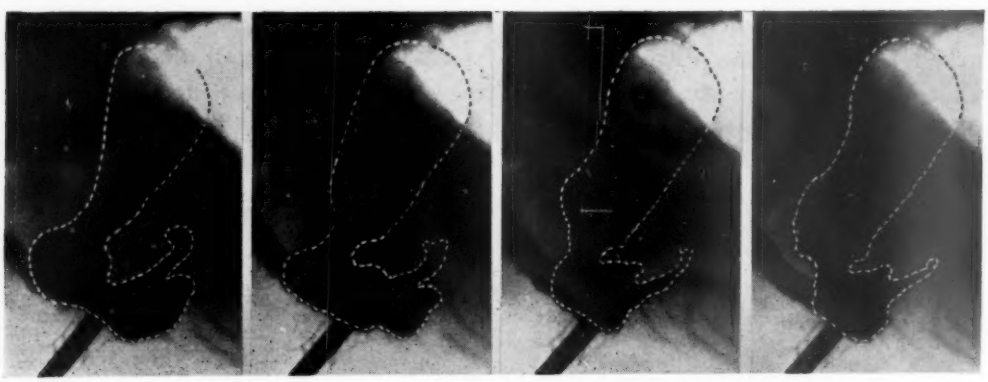

Fig. 3.—Cinefluorographic evidence of returning gastric motility in dog 5, 14 weeks after phrenicovagus anastomosis. A thin barium sulfate suspension was introduced through the gastrostomy seen at the bottom of each frame. Time interval between frames shown above is 2.5 seconds.

The method of continuous electrical stimulation would appear to be self-limited with respect to duration of the experiment. No such objection, however, is apparent in the phrenicovagus anastomosis. The demonstration that this is a feasible procedure, and therefore a potentially valuable tool for further studies of hypervagotonia, constitutes the most significant contribution of this study. In this connection the recording of action potentials simultaneously from the intact phrenic and from the vagus nerve distal to the anastomosis seems conclusive evidence of successful functional anastomosis. The gastric secretory and motor changes, corresponding qualitatively as they do to the effects of direct electrical and insulin stimulation, constitute further confirmatory evidence of the success of the procedure and the fact that the end organ is affected.

The fact that in dog 2 electrical stimulation beyond five hours became ineffective and that electrical stimulation failed to elicit any response at all after the fifth day is difficult to interpret. The fact that nonpolarizable electrodes were not used may be involved and edema of the nerve within the unyielding chamber, although not grossly apparent at autopsy, may have contributed to

the final failure to respond. It is even more difficult to interpret the rather erratic secretion in dog 5 after phrenicovagus anastomosis. The appearance of free acid and the rise in total acid in spontaneous secretion plus a negative insulin test can only be interpreted to mean that phrenic impulses were traversing the distal vagus nerve.

On the basis of this study, however, involving as it does a small number of animals, no definitive inferences concerning the gastric reaction to prolonged hypervagotonia can be drawn. What has been shown is that phrenicovagus anastomosis is a feasible and potentially valuable procedure which justifies further study.

SUMMARY

Hypervagotonia was accomplished by direct stimulation of the nerve by means of indwelling electrodes and by anastomosis of the proximal phrenic nerve to the distal vagus nerve in the thorax. Electrical evidence of successful functional anastomosis and evidence of gastric hyperfunction was obtained with the latter procedures. Motility was studied by means of cinefluorography and changes in response to phrenicovagus anastomosis were demonstrated. No information regarding the role of the vagus nerve in peptic ulcer pathogenesis was obtained.

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GASTROJEJUNAL ULCER

A Ten-Year Study

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GASTROJEJUNAL ulceration is one of the most serious sequela of surgery for peptic ulcer. It may present a difficult and, at times, a seemingly insoluble therapeutic problem. These ulcers occur in from 15 to 33 per cent of patients in whom a gastroenterostomy has been performed for duodenal ulcer, and from 3 to 8 per cent of cases in which a subtotal gastrectomy of the Billroth II type has been done.

Patients who present ulceration following gastroenterostomy, and to a lesser degree following subtotal gastrectomy, do not as a rule respond to medical treatment. They eventually require further surgery in which the mortality is appreciable, the morbidity considerable, and further recurrence of the disease is not unusual.

The purpose of this presentation is to review all operative cases of gastrojejunal ulcer from the ward and private services of the senior surgeon during the years 1940 to 1950. Seventy-nine patients were treated during this ten-year period. The group consisted of 69 men and 10 women whose ages averaged 48 years and individually varied from 25 to 69 years. These patients had had ulcer symptoms for from 3 months to 30 years prior to surgery, and the interval of good health between the primary operation and the first evidence of recurrence averaged 5.2 years, but varied between 10 days and 24 years. The most frequent symptom of gastrojejunal ulceration was pain, occurring in 59 of the cases. It was usually severe, and located in the midepigastrium, the periumbilical region, or the left upper or lower quadrants with radiation to the shoulder, the back, and the lower abdomen. The pain at times was periodic and relieved by food and alkalies. Occasionally it was continuous and not even benefited by medication. In two instances the pain was caused by an acute perforation of a previously unsuspected gastrojejunal ulcer.

Severe bleeding, either hematemesis or melena, was associated with pain in 27 patients, but was the sole symptom in 14. Other symptoms included vomiting (12 cases), diarrhea (8 cases), weight loss and dehydration.

The physical examination presented little of diagnostic value. The devitalizing effects of inadequate diet, bleeding, repeated vomiting and diarrhea, were evidenced by loss of weight and dehydration. Abdominal tenderness was usually present, located often in the left upper abdomen, but frequently in the epigastrium and periumbilical region. X-ray examinations revealed persistent patches of barium near the stoma, a deformity of the adjacent jejunal mucosal pattern, or progressive narrowing of the stoma in most cases. Gastroscopy, which was performed upon 17 patients, was rarely of diagnostic value. A

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jejunal ulcer or erosion was visualized only twice. Peristomal gastritis was seen in 5, diffuse gastritis in 3, a normal stoma in 5, and in the remaining 2 the examination was unsatisfactory.

Test meals invariably revealed the presence of free hydrochloric acid, and in many instances these values were exceedingly high. Anemia, hypoproteinemia, hypochloremia and alkalosis were frequent and mirrored the severity of the antecedent bleeding and vomiting. Stool examinations were usually positive for occult blood.

The cases in this series are divided into two groups: (1) gastrojejunal ulcers following gastrojejunostomy, and (2) gastrojejunal ulcers following subtotal gastrectomy of the Billroth II type (Table I).*

TABLE I. OPERATIONS PERFORMED FOR GASTROJEJUNAL ULCER, 1940 TO 1949

	Group 1	
Gastrojejunal ulcers following gastroenterostomy; 42 patients,† 43 operations	Subtotal gastrectomy	24
	Subtotal gastrectomy plus bilateral vagotomy	10
	Vagotomy as a sole procedure	7
	Jejunostomy as a sole procedure	1
	Separation of gastroenterostomy, subsequent subtotal gastrectomy	1
	Group 2	
Gastrojejunal ulcers following subtotal gastrectomy; 31 patients,† 41 operations	Additional gastric resection	16
	Vagotomy as a sole procedure	22
	Jejunostomy	3
Gastrojejunocolic fistulas following gastroenterostomy; 8 patients	Subtotal gastrectomy and closure of fistulas	5
	Staged procedures	3

†Two patients fall into both groups. The total number of patients was 79.

GROUP 1. GASTROJEJUNAL ULCERS FOLLOWING POSTERIOR GASTROENTEROSTOMY

There are 42 patients in this group, one of whom was operated upon twice so that 43 operations were performed. Exploration usually revealed numerous intra-abdominal adhesions secondary to previous procedures and inflammation. In some the lesion was represented by scar tissue which at times caused stenosis of the stoma or adjacent jejunum. In others, a diffuse acute inflammatory mass was encountered. The ulcer was gastric in 3 cases, stomal in 18, and jejunal in 11 (7 of which were in the efferent loop, 3 in the afferent loop, and 1 opposite to the stoma). In the remainder, the exact location was not identified. Seven cases presented a markedly stenotic functionless stoma. In these an active duodenal ulcer was present.

The procedure of choice in these cases was subtotal gastrectomy of the Billroth II type, which was performed in 34 patients. The operative technique has been fully described in a previous report.[1] The gastroenteric stoma is mobilized first by careful dissection, especially in the region of the middle colic artery. Following separation of the stomach from the jejunum, the gastric defect is closed to prevent soiling during the remainder of the procedure.

*Eight cases of gastrojejunal colic fistula following gastrojejunostomy will be considered separately.

Intestinal continuity is restored preferably by transverse jejunorrhaphy unless the removal of the ulcer necessitates a jejunal resection. At this stage the operation may be terminated if the patient's condition is unsatisfactory. This was deemed necessary in only one case. In the others, a subtotal gastrectomy was performed, and in 10 of these a bilateral infradiaphragmatic vagotomy was added. In 7 cases in Group 1, vagotomy alone was employed mainly to evaluate its efficacy. This was done via the transthoracic route in 2, and via the abdominal approach in 5. The latter is now preferred because it permits exploration and additional surgery if necessary. In one case, a patient with a severe cardiac condition, jejunostomy for alimentation was performed. The postoperative complications encountered in Group 1 in which subtotal gastric resection was performed, are summarized in Table II. It will be noted there were 4 deaths; 1 was presumed to be cardiac in origin. Post-mortem examination which was obtained in the other 3, revealed that the cause of death was pulmonary complications in 2, and generalized peritonitis of undetermined etiology in 1. In the 7 cases treated solely by vagotomy, there was 1 with a postoperative complication—bronchopneumonia—from which the patient recovered.

TABLE II. POSTOPERATIVE COMPLICATIONS IN 34 CASES OF GASTROJEJUNAL ULCER FOLLOWING GASTROENTEROSTOMY; TREATED BY SUBTOTAL GASTRECTOMY

COMPLICATION	NUMBER	RESULT
Atelectasis and bronchopneumonia	4	1 Fatality* 3 Recovery
Pulmonary embolus	1	Fatality*
Cardiac failure	1	Fatality
Generalized peritonitis	1	Fatality*
Subhepatic abscess	1	Recovery
Intestinal obstruction caused by		
Adhesions	1	Recovery
Jejunostomy	1	Recovery
Gastric ileus	2	Recovery One after 22 days One after 25 days
Hepatitis	1	Recovery
Gastric hemorrhage	1	Recovery
Wound infection	2	Recovery
Phlebitis	2	Recovery

*Post-mortem examination performed.

The follow-up results are based upon personal examinations which have been made over a period of from 1½ to 11 years (Table III). Of the 31 survivors following gastric resection, 29 have been followed. Twenty-three have remained well. Six have had recurrent ulcerations, 3 within the first year, and the remainder during the third year. One of the 6 recurrent ulcerations occurred in a patient in whom infradiaphragmatic vagotomy and subtotal gastrectomy were combined.

Six of the seven patients treated solely by vagotomy have been followed from 3 to 4½ years. There have been recurrences in 2 patients. On of these experienced severe melena a year after vagotomy. A subtotal gastric resection

was then performed with a good result, and the patient has been well for the past 3½ years. The second patient developed severe ulcer pain 9 months after operation, and 2 years later massive hemorrhages. He has refused further surgery.

TABLE III. FOLLOW-UP RESULTS IN GASTROJEJUNAL ULCERS FOLLOWING GASTROENTEROSTOMY

OPERATION	WELL		RECURRENCE		TOTAL
	NO.	PER CENT	NO.	PER CENT	
Subtotal gastrectomy	15	75	5	25	20
Subtotal gastrectomy plus vagotomy	8	89	1	11	9
Bilateral vagotomy alone	4	67	2	33	6
Jejunostomy for alimentation			1*	100	1

*Recurrence after 2 years.

There were 2 poor-risk patients previously mentioned in whom palliative procedures were done. The first patient developed a painful gastric ulcer within 4 months following the separation of the gastroenterostomy. A subtotal gastrectomy was performed and he has been well 8½ years. The second patient treated by jejunostomy for alimentation employed jejunal feedings to supplement oral intake for 1 year. During this time she had one mild episode of painless melena. The jejunal tube was then removed, but after 1 year further symptoms recurred. She has since been lost to follow-up.

GROUP 2. GASTROJEJUNAL ULCERS FOLLOWING SUBTOTAL GASTRECTOMY

In this group are 31 patients. All had a previous gastric resection and, in addition, many had had several antecedent procedures such as a gastroenterostomy, vagotomy, or jejunostomy. Exploration in these cases revealed pathology similar to that noted in Group 1. In addition, the region of the duodenum was always carefully searched for the presence of the pylorus and antrum. This condition was found on 2 occasions and examination disclosed intramural abscesses in 1, and gastritis in the other.

Surgical judgment may be sorely taxed in the cases in this group. In most of these patients the question arises as to the necessity of additional gastric resection. Whether this should be done depends upon two major factors. The first is the presence of a large residual gastric segment due to a previous inadequate gastrectomy. The second is an active penetrating or obstructing ulcer which so involves the gastrojejunal stoma that a further resection of the jejunum and stomach is necessary. For one or the other of these reasons a secondary gastric resection was performed on 16 patients, and in 4 an infradiaphragmatic vagotomy was added. In these, the postoperative complications included 2 instances of atelectatic bronchopneumonia, 1 of gastric retention, 1 of a left upper quadrant suppuration, and 1 of severe diarrhea. There were 3 deaths; 2 resulted from a generalized peritonitis, secondary to a dehiscence of the gastrojejunostomy. The third had a localized abscess which drained through the wound, and, in addition, extensive bronchopneumonia and toxic hepatitis. The 13 surviving patients were followed for periods varying from 1 to 11 years. Nine have re-

mained well. One of these lost considerable weight and presented a severe nutritional problem for over a year, but since then has improved. There were 4 who developed recurrent ulcers (Table IV).

TABLE IV. FOLLOW-UP RESULTS IN GASTROJEJUNAL ULCERS FOLLOWING SUBTOTAL GASTRECTOMY

OPERATION	WELL		RECURRENCE		TOTAL
	NO.	PER CENT	NO.	PER CENT	
Additional gastric resection	9*	69	4	31	13
Vagotomy alone	10	59	7	41	17

*Combined with infradiaphragmatic vagotomy in 4 cases.

Bilateral subdiaphragmatic vagotomy as a solitary procedure was performed by us, in 1939, in 2 cases of jejunal ulcers following subtotal gastrectomy.[1, 6] Since 1940, bilateral vagotomies were done on 18 patients, half by the transthoracic, and half by the abdominal, approach. The postoperative complications included moderate pleural effusion in 6 cases, and 1 instance each of severe intercostal nerve pain, gastric atony, intestinal obstruction, wound infection, and severe diarrhea. There has been no mortality since 1940.

All 18 cases have been followed. One died 3 months after operation from an unknown cause. Of the remainder, 10 have been well or markedly improved. Seven have been failures. In one the ulcer persisted, and in the others, recurrences were observed in 1, 4, 4, 7, 9 and 33 months, respectively. Four patients on whom the insulin test was positive were subjected to a second operation in a further attempt to effect complete vagotomy. In 3 of these patients, a transthoracic vagotomy was done first, and the second attempt was made via the abdominal route. In the fourth the order was reversed. In all four cases, in spite of 2 attempts to divide the vagi completely, the insulin test still remained positive.

There were 3 cases in Group 2 treated solely by preliminary jejunostomy for alimentation because the edema and exudation about the ulcer was so extensive that radical surgery was impossible. In 1 patient jejunal alimentation was continued for several weeks and then the tube was removed. That patient remained well for 1 year, at which time the ulcer recurred. Infradiaphragmatic vagotomy was performed 5 years later. The second patient was temporarily improved but jejunal alimentation had to be discontinued because of intolerance to feedings. Six months later a further resection was done in another hospital. This terminated fatally. The third case was not benefited by jejunostomy.

GASTROJEJUNOCOLIC FISTULAS

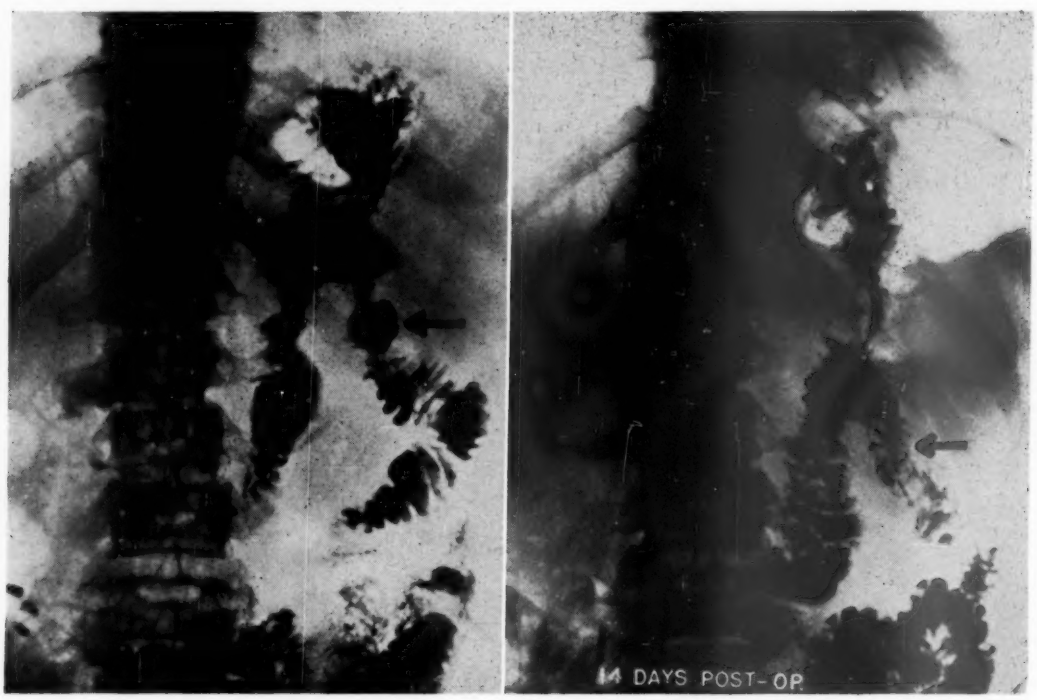
During this 10 year period, 8 cases with this severe complication of ulcer disease were treated surgically.* All of these patients were men whose ages varied from 37 to 69 years. Gastroenterostomy had been performed in each for peptic ulcer from 3 to 28 years prior to onset of this illness. The outstanding symptom was diarrhea which varied in intensity from a few to 20 watery

*Reference is made to previous reports from this Clinic by Dr. Percy Klingenstein on the management of gastrojejunocolic fistulas.[2]

Fig. 1 (M. E.).—*A*, Gastrojejunal ulcer following subtotal gastrectomy. *B*, Fourteen days after vagotomy, showing marked reduction in size of ulcer. *C*, Recurrent jejunal ulcer after vagotomy. *D*, After secondary gastric procedure, showing extremely high resection.

stools a day. The second most common and distressing symptom was fecal vomiting or foul eructations due to passage of colonic content into the stomach. There was marked loss of weight in all. None of these patients had the usual ulcer pain once the above symptoms began although several had periodic episodes of pain prior to onset of the diarrhea.

Two tests establish the diagnosis unequivocally. The simplest is the prompt recovery through a gastric tube of a methylene blue solution enema. The other is x-ray examination following barium meal or enema. In the former, the colon is outlined by barium passing directly from the stomach or perhaps from the upper jejunal loops. In the latter, the barium enema visualizes the stomach. One or both of these examinations were positive in all cases.



A. *B.*

Fig. 2 (E. I.).—*A*, Gastrojejunal ulcer following subtotal gastrectomy. *B*, Fourteen days after vagotomy, showing disappearance of ulcer.

At operation all of these cases presented numerous intraperitoneal adhesions. In some of the cases there were large inflammatory masses involving the area of the stoma, the colon, and the transverse mesocolon. The gastrojejunal ulcers were located at the stoma in 4 instances, and in the jejunum in 3, and in 1 the location could not be determined. The left side of the transverse colon was usually involved and in 2 instances the colonic penetration was almost at the splenic flexure. The duodenal ulcers were healed except in 1 case which will be described later. The operative procedures varied with the existing pathology and the condition of the patient. In 5 instances it was possible to separate the gastroenterostomy, repair the defects in the colon and jejunum,

and then perform a subtotal gastric resection. Four of these patients have been well for from 4 to 7 years. One, however, developed severe bleeding 6 years later when an additional gastric resection and vagotomy was done elsewhere.

In the remaining 3 cases, the desired complete definitive procedure could not be carried out in 1 stage. One patient, a man of 57 years, was in exceptionally poor nutritional state. A preliminary ascending colostomy was performed. This did not help the nutritional status, however, and at the second operation the gastroenteric stoma was taken down and the colonic fistula closed. The duodenal ulcer was noted to be inactive. Shortly thereafter the colostomy was closed. The patient did well for 10 months, then he developed a recurrence of a duodenal ulcer. Subsequently a subtotal gastrectomy was performed. He has been well for 9 years. The second case, which required a staged procedure, concerned a 39-year-old man with a huge jejunocolic fistula. A preliminary ascending colostomy was performed. One month later a subtotal gastrectomy and a colonic resection were performed. The postoperative recovery was good and subsequently colostomy closure was done. Soon thereafter he was lost to follow-up.

The third case was a 69-year-old man in whom extensive surgery was precluded by the physical condition. Therefore the gastroenterostomy and colon were disconnected, followed by closure of the defects in the stomach, colon, and jejunum. The patient made a good operative recovery, but two months later developed substernal pain and x-rays revealed a peptic esophagitis. Four months later severe abdominal pain occurred and a large duodenal ulcer was demonstrated by x-ray. He was re-explored and both the duodenal ulcer and peptic esophagitis were confirmed. A posterior gastroenterostomy was performed without complication. Ten months later he was admitted elsewhere because of marked dysphagia for which a preliminary jejunostomy for alimentation was done. This was followed by an esophagogastrectomy which resulted in death.

DISCUSSION

Prior to 1923, one of the most popular and effective procedures for duodenal ulcer was gastrojejunostomy. This simple operation which provides drainage in cases of pyloric obstruction and permits partial neutralization of the free acid by regurgitation of the alkaline duodenal content, usually results in healing of the lesion with relief of the symptoms. Unfortunately, gastrojejunal ulceration, manifested by pain, bleeding, and occasionally perforation, follows in 15 to 33 per cent of cases. In order to diminish the incidence of this serious complication, the operation of subtotal gastrectomy was devised which causes a marked reduction in acidity by the elimination of the chemical phase of gastric secretion. The clinical results in the majority of patients are excellent. There is, however, a small percentage of failures. The Billroth II type of gastric resection, favored in this country, is still complicated by gastrojejunal ulceration in 3 to 8 per cent of the cases. Some of these recurrences may be ascribed to errors in operative technique. One of these is the inadequate removal of the acid-secreting glands of the stomach. In order to remove the entire antrum and sufficient area of the corpus, it is generally considered that at least two-

thirds of the stomach must be resected. However, Smithwick has shown that the removal of more than two-thirds of the stomach plays an unimportant role in the prevention of gastrojejunal ulceration.[3] In other cases recurrences may be ascribed to the fact that a "prepyloric ausschultung" was done. In these cases the retained pyloric and antral mucous membrane still produce secretin which is responsible for the continued chemical phase of gastric secretion, a factor in the production of gastrojejunal ulcer.

However, there are cases in which these basic requirements have been met and yet recurrences develop. The reasons for these failures are speculative but the only common denominator in all these cases is the presence of free hydrochloric acid. Why all patients who still have free acid after subtotal gastrectomy do not develop ulceration is enigmatic. However, it is now well recognized that ulceration in the presence of anacidity is exceedingly rare. If a persistent anacid state in the ulcer patient could be maintained regularly by some method, the problem of recurrent ulceration would become insignificant.

Once a gastrojejunal ulcer has developed, conservative medical management is rarely effective, and surgery, in spite of the risk and the possibility of further recurrence, seems to offer the best results. For gastrojejunal ulcers following gastroenterostomy, the type of operation to be chosen should be dictated by two considerations: (1) which procedure will insure the greatest protection against further recurrence, and (2) will this procedure, which is an extensive one, be tolerated by the patient? The greatest protection against further recurrence in this series was most frequently attained by a combination of subtotal gastrectomy and vagotomy. Similarly, in a series of 130 primary duodenal ulcer cases treated by subtotal gastrectomy combined with vagotomy, there were no recurrences in cases followed from 6 months to 5 years. During the same period there were 9 recurrences in 189 cases of duodenal ulcer subjected solely to subtotal gastrectomy.[7] Unfortunately, many patients suffering from gastrojejunal ulcer are poor operative risks and lesser procedures must be substituted. In these, vagotomy alone should be done despite the fact that the incidence of recurrence is definitely higher.

In gastrojejunal ulceration following subtotal gastrectomy, the choice of operation is even more difficult. The existence of a previous inadequate resection or the presence of an extensive penetrating or obstructing jejunal ulcer makes further resection mandatory provided the condition of the patient is satisfactory. Whenever possible, this should be combined with an infradiaphragmatic vagotomy. However, in patients who will not tolerate additional resection, vagotomy alone is indicated. In some of our cases this was followed by a marked reduction of the acidity with disappearance of the ulcer.[4] In other cases there was a temporary relief of symptoms but the ulcer reappeared in a short time. Jejunostomy for alimentation may be employed to tide extremely debilitated and emaciated patients over critical periods. It is regarded as a preliminary measure to be followed by a more definitive procedure when the physical condition of the patient improves.[5] Jejunojejunostomy is mentioned only to be condemned. It is at times a tempting procedure when obstruction of the afferent

loop is present. Although the obstruction may be relieved by this procedure, further exacerbation of the ulcer will certainly follow diversion of the alkaline biliary and pancreatic secretions.

In the evaluation of results of any therapy for peptic ulcer, it must be recognized that once an ulcer has developed, it may recur at any time during the life of an individual. In this group of cases, the average time of onset of a stomal ulcer after the primary operation was 5 years. In many cases it was much longer, and in one the interval of well-being was 24 years. Therefore, follow-up results of any surgery for gastrojejunal ulcer which are less than 5 years can, at most, only suggest trends and do not warrant definite conclusions. This point must be remembered, especially in the evaluation of vagotomy in this series in which the periods of observation are shorter than those following gastric resection.

When Group 1 and Group 2 are compared, the poorer results obtained in the surgery for gastrojejunal ulcers following subtotal gastrectomy are striking. The reason undoubtedly lies in the fact that in Group 1 the jejunal ulcer followed an inadequate primary operation, gastroenterostomy, whereas in Group 2, an even more radical procedure, subtotal gastrectomy, was ineffective. Therefore the patients in Group 2 must represent a more severe form of ulcer disease. In this category there were a few patients who developed recurrence after recurrence despite a multiplicity of operations including several gastric resections, vagotomy, or both combined. In these patients there was always the persistence of gastric secretion high in its content of free hydrochloric acid. A total gastrectomy may be the only operation which eliminates this condition. Nevertheless, in one patient in our series, in which this procedure was finally resorted to elsewhere, a subsequent exsanguinating fatal hemorrhage occurred, possibly due to the presence of ectopic gastric mucous membrane in the esophagus.

SUMMARY AND CONCLUSIONS

1. All patients operated upon for gastrojejunal ulcer during a ten-year period have been reviewed. Forty-two followed gastroenterostomy and 31 followed subtotal gastrectomy. There were eight gastrojejunocolic fistulas.

2. The clinical features, pathologic findings, operative procedures, and follow-up results are described.

3. Follow-up observations indicate that subtotal gastrectomy combined with vagotomy still offers the best results for gastrojejunal ulcers following gastroenterostomy. In gastrojejunal ulcers following subtotal gastrectomy, further gastric resection combined with infradiaphragmatic vagotomy will offer the best protection against further ulceration.

4. Vagotomy as a solitary procedure is recommended in poor-risk patients.

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POSTOPERATIVE PAIN; ITS USE IN THE COMPARATIVE EVALUATION OF ANALGESICS

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OUR original interest in this problem was with the testing of the analgesic activity of a new nonnarcotic compound. It soon became evident, however, that the most useful information forthcoming from the study was a better understanding of the nature and incidence of postoperative pain. It will be demonstrated that the frequency and severity of postoperative pain have, in general, been overemphasized. The use of this type of clinical pain, therefore, has serious pitfalls in the evaluation of analgesic agents.

METHODS

Unselected ward patients subjected to a variety of surgical procedures were the subject material for this study. Pain was accepted as real in all instances when volunteered by the patient upon hourly bedside visits. No attempt was made to interpret psychological factors in the reporting of pain by the patients. Nurses were instructed to administer morphine or meperidine if the patient complained of pain, but to administer no drug unless such complaint was forthcoming. The patient was not informed about the expectation of pain following operation. However, it appears to be commonly accepted that recovery from operation is painful. There is no reason to suppose that the patients studied were not exposed to the expectation of pain. No member of the operating team or the recording observer was aware of whether analgesic agents were employed during operation or following its completion.

The criteria for the rating of postoperative pain were as simple as possible. Pain was considered absent if analgesic drugs were not required postoperatively, as moderate if a maximum of two doses of a potent analgesic drug (morphine or meperidine) was required within a 24 hour period, and as severe if more than two doses of a potent narcotic were required in each 24 hour period. These criteria are considered to be conservative, reasonably objective, and rigid.

The original purpose of designing these experiments was the testing of the analgesic potency of diethylaminoethanol (DEAE). It had been reported that

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procaine given intravenously relieved postoperative pain[1] and there was the possibility that procaine exerted its characteristic actions through its metabolite DEAE.[2]

RESULTS

A total of 286 patients were studied. The first group, which contained 118, received 2 to 4 Gm. of DEAE intravenously at the end of general anesthesia. Table I summarizes the data. These data examined alone would appear to indicate that DEAE has significant analgesic activity.

TABLE I*

	ABDOMINAL AND THORACIC SURGERY	SURGERY OF SUPERFICIAL PARTS OF BODY	TOTAL OF ENTIRE GROUP
No pain	18 (30%)	40 (69%)	58 (49%)
Moderate pain	20 (33%)	15 (26%)	35 (30%)
Severe pain	22 (37%)	3 (5%)	25 (21%)
Total	60	58	118

*2 to 4 Gm. DEAE given intravenously at end of anesthesia.

One hundred nineteen unselected patients were used as controls in the course of the study of DEAE. Saline was administered to these patients intravenously at the end of anesthesia. The "analgesic" power of saline, as shown in the summary in Table II, is not significantly different from that of DEAE.

The patients undergoing abdominal and thoracic surgery, traditionally, are supposed to experience considerable postoperative pain. However, 50 per cent of these patients did not require more than 2 doses of a potent narcotic agent for 24 hours, 23 per cent required no analgesic material in the postoperative period, and 27 per cent were maintained in comfort by more than two doses of morphine or meperidine for each 24 hour period (Table II).

TABLE II*

	ABDOMINAL AND THORACIC SURGERY	SURGERY OF SUPERFICIAL PARTS OF BODY	TOTAL OF ENTIRE GROUP
No pain	11 (23%)	35 (49%)	46 (38%)
Moderate pain	13 (27%)	29 (41%)	42 (35%)
Severe pain	24 (50%)	7 (10%)	31 (27%)
Total	48	71	119

*Saline placebo administered at end of operation.

Another study was carried out on subjects who had complained of postoperative pain. The clinical material was as uniform as possible, involving 49 patients in the fourth decade of life who had been subjected to hysterectomy by a uniform technique carried out through a low midline incision and who complained of severe postoperative pain. An observer remained at the bedside of each patient during the operative day. Without comment or communication to the patient, an intravenous injection of 5 c.c. of saline solution was given upon the first complaint of pain. If the pain was not relieved within 30 minutes, a subsequent intravenous injection of 10 mg. of morphine diluted to

5 c.c. in saline was then carried out. In this group of patients it was found that 32 (65 per cent) obtained relief from the administration of saline. Of the remaining 17 (35 per cent), 15 required morphine and obtained satisfactory pain relief. Two of these were resistant to morphine as well as to saline.

DISCUSSION

The results reported here are unexpected. It seems clear, though, that the pain following operation is neither invariable nor necessarily severe. Approximately one-third of the patients in these studies had no pain in the postoperative period sufficiently severe to elicit a complaint. Even patients who do complain of pain postoperatively may have significant pain relief by the administration of a placebo.

These data suggest that extensive analgesic therapy postoperatively is unnecessary as a routine measure. Patients, after operation, can be cared for with respect to pain relief by measures other than potent narcotic administration in a majority of instances. These, of course, include attention to nursing comfort, the awareness of psychological factors implicit in the postoperative convalescence, and other measures of a similar nature.

It is evident that if pain is severe in only approximately one-third of patients following operation, such clinical material is somewhat less useful for the study of analgesic agents than has been recognized heretofore. The data emphasize the need for rigidly controlled experiments if this type of subject is utilized. Patients whose pain is placebo sensitive should be screened out in such studies by the prior administration of a placebo before testing the effectiveness of an unknown analgesic material.

SUMMARY

1. Studies have been reported on the nature and severity of pain following surgical procedures.

2. By a variety of methods, it has been demonstrated that significant and real pain following surgical operation is present only in approximately one-third of patients subjected to operation. Furthermore, one-third of the patients operated upon have no significant pain. A final third have pain which is moderate and easily relieved by infrequent doses of narcotics.

3. Caution in interpretation is necessary when postoperative patients are used for the study of analgesic agents and methods if the application of these findings to the therapy of painful states is to be on a firm experimental basis.

The authors wish to express appreciation to Dr. John Atkinson and Dr. Martin Helrich for observing some of the patients reported in this study.

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Case Reports

SQUAMOUS-CELL CARCINOMA OF THE AMPULLA OF VATER

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ENTHUSIASM for radical surgery in lesions of the pancreas appears to have abated considerably. It is, however, generally conceded that the lesion most suitable for pancreatoduodenectomy is a carcinoma of the ampulla of Vater. These growths are small, often so small as to escape detection, and very rarely exceed 3 cm. in size. It is usually impossible to determine the exact origin of the tumors, but they may arise from the papilla of Vater, or the terminations of the common bile duct or pancreatic duct. Because of their strategic position they usually attract attention early enough to make radical excision feasible. The onset of this process is usually with jaundice which may be intermittent in character and often is accompanied by pain simulating gallstone colic. It is therefore not uncommon that the clinical impression is that of common duct stones. Even at operation the diagnosis is not always apparent and may not be made without duodenotomy. The vast majority of ampullary lesions are adenocarcinomas, papillary or scirrhous in type. Squamous metaplasia appears to be quite a rarity and little or no mention of it is made in the literature.

Because squamous carcinoma in this location is so uncommon the following case is recorded.

CASE REPORT

E. S., a 68-year-old white woman, was admitted to the Swedish Hospital with a diagnosis of obstructive jaundice of moderate degree. A history of recurrent attacks of biliary colic for the preceding seven years was obtained. A recent cholecystogram had revealed a nonfunctioning gall bladder. Laboratory studies indicated the presence of obstructive jaundice with normal liver function. The preoperative impression was choledocholithiasis. However, because the patient had a clearly palpable enlarged gall bladder, a neoplastic obstruction of the common duct could not be excluded. At laparotomy a distended gall bladder and duct system were found. The common duct was opened. Bakes dilators were found to pass easily into the duodenum. A bean-sized mass was palpable at the ampulla. This was interpreted as a calculus impacted in the wall of the duct which could not be dislodged. Duodenotomy was performed and the papilla incised. It was now apparent that we were dealing with a small papilliferous tumor of the ampulla as the obstructing agent. A radical pancreatoduodenectomy was thereupon performed following the now standardized technique except that for technical reasons the gall bladder instead of the choledochus was anastomosed to the jejunum.

The excised mass consisted of the pyloric end of the stomach, the duodenum, and the head of the pancreas. The distal 5 cm. of the common bile duct were included. The opened specimen revealed normal gastric and duodenal mucosa. The ampulla of Vater was dilated

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Fig. 1.

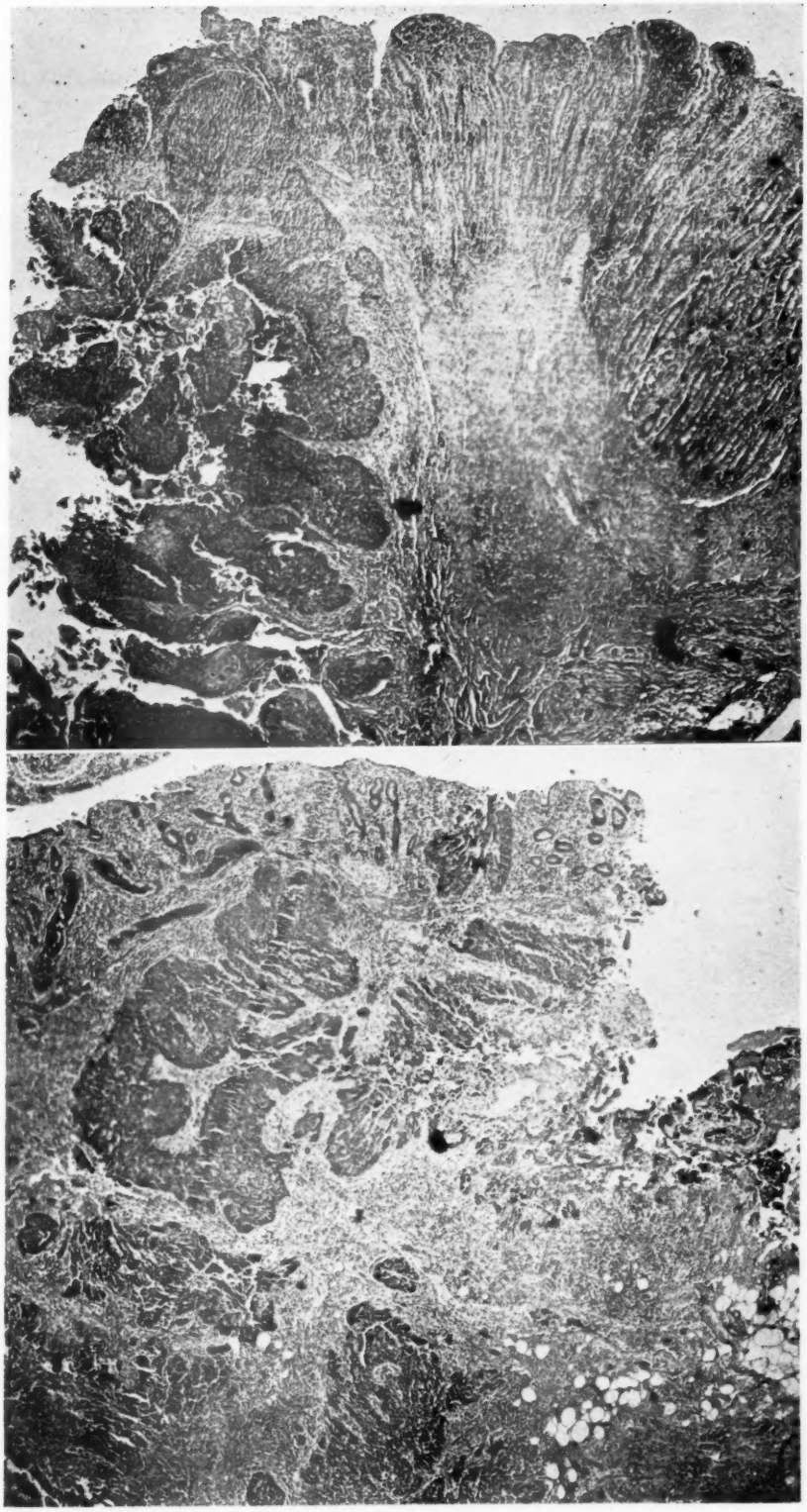

Fig. 2.

Fig. 1.—Section through the edge of the ampullary ostium showing invasion of the duodenum by the squamous-cell carcinoma. Areas of cornification are seen in the lower left-hand corner (×30).

Fig. 2.—Section through the terminal part of the common bile duct with invasion by surrounding tumor (×30).

to 1 cm. in diameter and the orifice was surrounded by a raised fringe of grayish, ragged tissue. The common bile duct was dilated and had a moderately thickened wall with a flattened, fibrotic mucosa. No stones were present. On the serosal side, just before the duct entered the duodenal wall, there was an ovoid nodule measuring 2 by 1.5 by 1 cm.; the cut surface of this showed white granular firm tissue with a dense fibrous reticulum and surrounding fibrous capsule. The head of the pancreas showed normal lobular structure. The pancreatic duct was dilated with a thin wall and smooth lining.

Microscopic Examination.—The ampullary sections show a squamous-cell carcinoma, many areas of which show cornification and epithelial pearls. No transition can be seen from the epithelium of the pancreatic duct or bile duct. In some sections the squamous cells are arranged in structures resembling glands.

The nodule shows a very well differentiated squamous-cell carcinoma with many pearls and areas of cornification surrounded by a fibrous capsule.

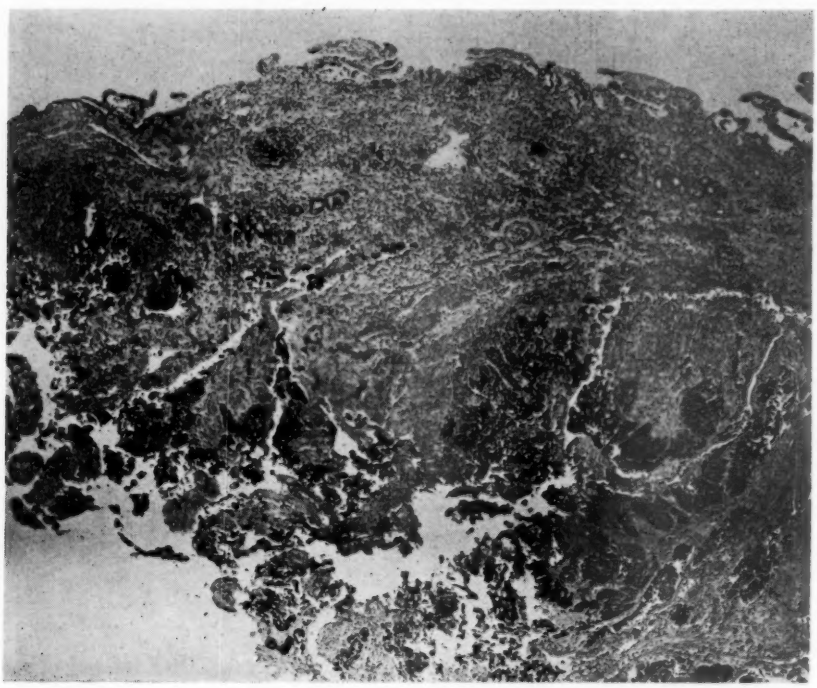

Fig. 3.—Section through terminal part of the pancreatic duct. In the lower right-hand corner there are glandlike structures composed of tumor cells. The cells are squamous in type (×30).

DISCUSSION

Squamous-cell carcinoma of the gall bladder is a well-known entity. Squamous-cell carcinoma of the extrahepatic bile ducts has been described in a case report by Cabot[1] although Willis[7] did not discover squamous metaplasia in 32 cases of extrahepatic biliary carcinoma. Marshall[4] reported 49 cases of biliary duct carcinoma all of which were adenocarcinoma. Fifteen of these cases were at the ampulla. Carcinoma of the ampulla of Vater is in itself rare and only a few cases of squamous-cell carcinoma of this region are on record. Kirshbaum and Kozoll,[3] reporting 62 cases of extrahepatic biliary carcinoma, described a squamous-cell carcinoma involving the papilla of Vater with ulceration into the duodenum. Mateer and Hartman[5] found two cases of adeno-

cancroid of the ampulla in a series of 9 carcinomas of this area. Cohen and Colp[2] reviewed 8 cases of carcinoma of the periampullary region of the duodenum; one of these showed squamous-cell carcinoma with lymph node involvement.

The pancreatic ducts are the site of squamous metaplasia and squamous-cell carcinoma can develop. These tumors are discussed by Nicholson,[6] and he also refers to cases of cancroid of the common bile duct.

Carcinoma of the ampulla of Vater can arise in the termination of either the pancreatic or the common bile duct. It is extremely unlikely that they arise in the duodenal mucosa itself. Our case, by its anatomic location, is undoubtedly a primary carcinoma of the ampulla of Vater of squamous-cell type. It is impossible to say whether it arose in the termination of the biliary or pancreatic duct but we feel that one of these is its origin, as these ducts are sites of squamous metaplasia.

SUMMARY

1. A case of primary squamous-cell carcinoma of the ampulla of Vater with regional node metastases is reported.

2. The origin is discussed.

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FEMORAL VEIN GRAFT FOLLOWING BILATERAL INTERNAL JUGULAR VEIN RESECTION

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SINCE Crile[1] wrote his first paper on radical dissection for metastatic carcinoma there has been considerable discussion on the dangers of bilateral ligation of the internal jugular veins. Crile, in his initial paper, reported one bilateral neck dissection in which both jugulars were ligated with no untoward results. Horsley,[2] in 1914, mentioned a case of radical neck dissection where the internal jugular vein was so large that he feared excision of this structure would impair venous return from the head; therefore he left the vessel intact. Also in the early literature we find a few scattered reports of severe postoperative complications or mortality following ligation of the second internal jugular vein. The most notable of these reports was that of Duval who was recently quoted by Sugarbaker.[3] Duval did a simultaneous bilateral ligation and immediately after the second ligation the patient's face became cyanotic and there was a sudden profuse hemorrhage from the mouth and throat. This patient eventually recovered. Because of such warnings the usual procedure in bilateral radical neck dissection is a staged operation which separates the first ligation from the second by several weeks to several months. Some authorities believe that the longer the second stage is delayed, the less likely it is that the patient will be faced with evidence of chronic venous obstruction, i.e., "fat face," pseudo cyanosis or edema of the eyelids. Modlin,[4] in presenting bilateral neck dissections for carcinoma of the tongue, stated that at the Ellis Fischel State Cancer Hospital the second side of the bilateral dissection is carried out in the same manner that an axillary dissection is done, in that the second jugular vein is preserved to prevent these possible postoperative complications. Jorstad[5] believes that the excessive manipulation necessary to save the internal jugular vein in this type of dissection leads to more difficulty than simple excision.

Gius[6] and Sugarbaker[3] have recently reviewed the routes of venous return from the head following bilateral neck dissection. Gius beautifully demonstrated the patent pathways via the vertebral plexus of veins after obliteration of the superficial system in stillborn infants by injection of opaque material into the superior longitudinal sinus. He did not feel that increased intracranial pressure played much part in the postoperative complications to bilateral neck dissection. Sugarbaker, on the other hand, attempted to demonstrate that ligation of the second internal jugular vein causes considerable increased intracranial pressure which he felt was the cause of death in two patients out of five bilateral staged neck dissections. More recently Martin[7] reported sixty-six patients who were subjected to staged bilateral radical neck dissections with no

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operative mortality. Furthermore he reported one patient who had a simultaneous bilateral radical neck dissection with no postoperative complications. Study of this patient revealed no appreciable rise in the spinal fluid pressure following ligation of the second internal jugular vein.

In discussing this problem with several experienced investigators[5, 8, 9] in this area, there has been complete agreement that postoperative morbidity and mortality will be much lower if staged radical neck dissections are done. It is also generally agreed that bilateral simultaneous radical neck dissections are rarely[4] indicated. We wish to report a case of bilateral simultaneous radical neck dissection done by one of us (E. M. B.) in which the continuity of the left internal jugular was re-established with a graft of the superficial femoral vein. The procedure was elected because the preoperative clinical impression did not coincide with the pathology found at the time of operation. It should be recorded that this procedure was mentioned as a possibility by Bronson Ray[6] in the discussion of Gius's paper on bilateral neck dissection.

CASE 176156.—E. B. D., a 60-year-old man, was admitted to Barnes Hospital on Sept. 29, 1949, with a biopsy-proved squamous-cell carcinoma of the cervical esophagus. On Oct. 4, 1949, the patient was subjected to resection of the larynx, pharynx, and the upper third of the esophagus.* The right lobe of the thyroid gland was preserved with the parathyroids intact. A tubed pedicle graft from the neck was made and anastomosed to the thoracic esophagus. The postoperative course was uneventful except for the development of stenosis at the site of the anastomosis with the thoracic esophagus. Subsequently, the patient was subjected to a series of procedures finally culminating in resection of the remaining thoracic esophagus and anastomosis of the stomach to the tubed pedicle reconstruction. Following this procedure the patient was able to eat quite normally but required daily dilatation of the anastomotic site which he was able to do for himself.

The patient was readmitted to Barnes Hospital on Nov. 9, 1950, appearing in excellent general condition but with evidence of bilateral metastases to the lymph nodes of the neck in the jugulo-digastric area. X-ray examination of the chest was negative for pulmonary metastases. Since there was no evidence of persistent or recurrent tumor elsewhere, it was decided that a bilateral radical neck dissection was indicated. The mass on the right side of the neck seemed to be fixed to the deeper structures while the mass on the left side was smaller and more freely movable.

On Nov. 15, 1950, the patient was taken to the operating room and a bilateral radical neck dissection was done. The right side of the neck was attacked first since the mass on this side of the neck was larger and it was felt it would be necessary to excise the internal jugular vein on this side. This impression was verified as the operation progressed. An uneventful anatomic dissection was accomplished with excision of the internal jugular vein from the level of the omohyoid muscle to the jugular bulb. The head was then turned and dissection of the left side of the neck was started. When the left internal jugular vein was exposed, it was found that the metastatic mass was inseparably attached to this vessel. A partial excision of the vein wall was attempted in order to maintain its continuity, but this resulted in such severe constriction of the vein, after it was repaired, that the return flow was inadequate. Dissection of the submaxillary triangle on this side was completed as rapidly as possible in spite of the fact that all visible venous tributaries became intensely distended and there was a continuous pouring of dark venous blood from all raw surfaces of the wound. Inspection of the patient's face beneath the drapes showed that it was a dark bluish color, the tongue was protuberant and there was considerable edema of the skin. The

*This operation and subsequent thoracic stages were done in collaboration with Dr. Thomas Burford of the Barnes Hospital Staff.

patient's condition was considered to be quite critical and it was therefore decided to re-establish the venous blood flow from the head by the insertion of a vein graft on the left side. Accordingly, a 5 cm. segment of the superficial femoral vein was removed from the left thigh, and the constricted segment of the internal jugular vein was excised. The femoral vein graft was then inserted with the valves facing inferiorly and it was anastomosed to the proximal and inferior segment of the internal jugular vein by a continuous everting suture of fine silk (Fig. 1). With patency of the left internal jugular system re-established, there was immediate cessation of venous blood oozing from the raw surfaces and the bluish

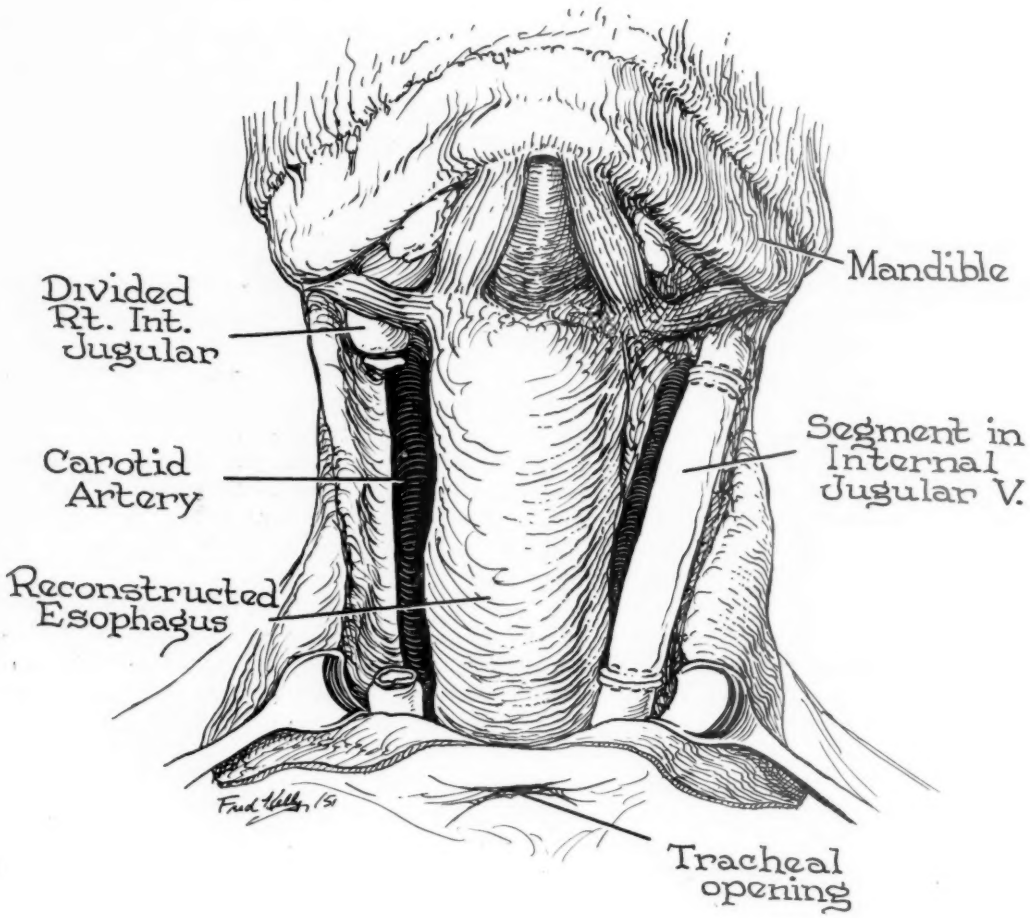

Fig. 1.—The vein graft illustrated is longer than that actually used. The superficial femoral vein was found to satisfactorily fit the lumen of the cut ends of the internal jugular vein. There was a remarkable contraction in length of the superficial femoral vein segment after it was excised. Obviously, this must be taken into consideration in measuring the segment of vein to be used for the graft.

discoloration of the face rapidly disappeared. The graft was obviously functioning quite effectively when the wound was closed. The postoperative course was uneventful. There was no more edema of the face than usually follows a bilateral upper neck dissection. The last communication from this patient and his physician was dated October, 1951, and indicated that he was free from any evidence of tumor; he was working steadily and was in a satisfactory state of health (Fig. 2). It is necessary for him to dilate his anastomosis daily with a dilator which he has learned to use with great facility. He eats an essentially normal diet. There have been no symptoms referable to removal of the vein segment from the thigh.

DISCUSSION

No effort has been made to determine whether or not the graft remained patent after the operation. However, there is no question in our own minds that the graft functioned effectively to reduce the immediate hazzard of the procedure and remained patent long enough at least to allow development of adequate collateral venous return from the head. It is admitted that bilateral simultaneous resection of the internal jugular vein will seldom be indicated, except in some unusual circumstances as in the case cited. Obviously the use of a vein graft as described will require preservation of enough of the distal vein stump to allow control of bleeding and the performance of the anastomosis. By using a Blalock clamp, as was done in this case, the anastomosis can be done to a vein stump extending from 3 to 4 cm. below the base of the skull.

Fig. 2.—The degree of swelling of the face after the first postoperative day was never any more than that usually encountered following a bilateral upper neck dissection in which both jugular veins are left intact. This patient is at present without evidence of carcinoma, two years following esophagectomy and one year following bilateral neck dissection with resection of the internal jugular veins.

SUMMARY

A case is reported in which a graft of superficial femoral vein was used to re-establish the continuity of the left internal jugular vein, thus relieving excessive venous congestion of the face and head resulting from bilateral internal jugular vein resection.

ADDENDUM

Since the submission of this paper for publication two additional articles on the subject of bilateral resection of the internal jugular vein have appeared in the literature. Morfit[10] has reported a case and points out the possible importance of controlling cerebrospinal fluid

pressure during the operation by removal of cerebrospinal fluid. He also emphasizes the importance of tracheostomy since upper respiratory obstruction may result from edema. Perzik[11] reports two cases of bilateral radical neck dissection with survival.

It is of interest that in our case, E. D., the insertion of the vein graft appeared to completely and immediately relieve the patient of the undesirable effects of bilateral internal jugular occlusion. It was not stated in the description of the operation, but the anterior and external jugulars were also sacrificed in this patient. At the time of the present writing, April 24, 1952, this patient is still well and without evidence of recurrence.

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AVULSION AND EMBOLIZATION OF A CALCIFIC ARTERIAL PLAQUE; FEMORAL EMBOLECTOMY

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THIS report deals with a case of acute occlusion of the common femoral artery resulting from embolization of a large calcareous plaque, presumably avulsed from the wall of the aorta. Embolectomy was performed, with recovery.

Heart disease is responsible for over 90 per cent of the cases of peripheral arterial occlusion.[1] Emboli may also arise from detached thrombi originating in aneurysms,[3] or on arteriosclerotic plaques, or as a result of arterial injury and inflammation.[2] They may also originate in the pulmonary vein,[1] or by the paradoxical embolization of a venous thrombus through a patent foramen ovale.

Recent reports have described the post-mortem finding of a systemic arterial embolization arising from eroded atheromata.[4-6] Flory[4] described pathologic lesions in small vessels as cholesterol emboli. Le Count[7] reported a case in which the coronary artery was occluded by loose lime masses that originated in softened atheromatous patches. To our knowledge there has been no report of the embolization of a large arterial plaque, en masse, occluding a major artery.

CASE REPORT

Mr. J. L., a 51-year-old knitting machine operator, was admitted to the Beth Israel Hospital Jan. 25, 1951, complaining of the sudden onset of severe pain in the right calf six hours prior to admission, followed by pallor and coldness to the junction of the middle and lower third of the right thigh.

In 1945 diabetes had been diagnosed, and he was treated with insulin and diet for one year. He had scarlet fever in childhood. Hemorrhoids had been noted for three years. There was no history of hypertension, angina, congestive heart failure, or intermittent claudication. He smoked one to two packages of cigarettes daily. The patient believed that he had been in good health until the morning of admission.

Examination upon admission disclosed a well-developed and well-nourished man in apparent acute distress, with blood pressure 160/84, temperature 99° F., pulse 90, and respiration rate 18 per minute. Urinalysis disclosed glucose 4 plus, but no acetone. The blood glucose was 230 mg. per cent. Prothrombin activity was normal. Examination of the blood revealed 15 Gm. of hemoglobin and 5,260,000 erythrocytes. The leukocyte count was 14,500 of which 69 per cent were polymorphonuclear cells.

Pupils were miotic (opiate), and the fundi were negative. The heart, lungs, and abdomen disclosed nothing significant. An electrocardiogram was normal. Hemorrhoids and prolapsed rectal mucosa were noted. The left lower limb was warm, and there were palpable pulsations in the femoral, popliteal, and dorsalis pedis arteries. The knee and ankle jerks were active. The right lower extremity was cold distal to the junction of the lower and middle third of the thigh. Good pulsations were felt for apporximately one inch below the right inguinal ligament, but not distal to this. Pallor, numbness, and absence of sensation to pin prick were noted over the area of coldness. Toe position sense was absent. There was inability to move the right foot and toes, and absence of deep reflexes at the knee and ankle. A diagnosis was made of right common femoral artery obstruction at its bifurcation, presumably due to an embolized aortic plaque.

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Following a paravertebral lumbar sympathetic nerve block with procaine over segments L_1, L_2 and L_3, there was immediate relief of calf pain. This suggested release of vasospasm,[2] although there was no change in either the color or temperature of the limb, and it was decided to continue conservative therapy for several hours.

The head of the bed was elevated, and the leg was protected by cotton wadding and placed under a cradle. A hot water bag was applied to the abdomen. An intravenous infusion of normal saline was started, and 0.2 Gm. papaverine and 0.1 Gm. heparin were injected into the tubing. Dicoumarin, 0.3 Gm., was given by mouth. Penicillin was injected intramuscularly.

Four hours following the institution of the above regimen it was felt that there had been no significant improvement in the circulation of the right lower extremity. While the superficial veins that had been totally collapsed now appeared to contain a slight amount of blood, all the other abnormal findings persisted, including the absence of oscillometric pulsations below the right inguinal region. The blood coagulation time was 40 minutes, and there was some oozing from the hemorrhoids. The patient was prepared for surgery, and a whole blood transfusion was started.

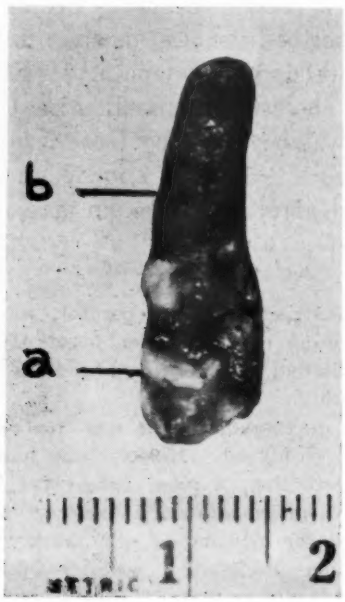

Fig. 1.—Embolus consisting of calcific tissue (*a*) and propagated thrombus (*b*).

Under general anesthesia, thirteen hours following the onset of symptoms, a right common femoral arteriotomy was performed. The embolus was situated at the bifurcation of the common femoral artery, which was pulsating proximally, but there were no pulsations in either the superficial or profunda femoral arteries. The embolus (Fig. 1) consisted of an irregular calcareous mass, not adherent to the intima, measuring 1 by 0.7 by 0.5 cm. At its proximal end there was an adherent fresh clot about 1 cm. long. The wall of the artery was not sclerotic, and the intima was smooth. Following the embolectomy, there was free bleeding from the three major vessels involved. The arteriotomy site was closed with number 00000 atraumatic silk sutures, and 0.04 Gm. of heparin was instilled into the vessel. A periarterial stripping of the three major vessels involved was performed. The wound was closed without drainage. No unusual bleeding was noted during the course of the operation. Pulsations were apparent immediately in the superficial and profunda femoral vessels, and the dorsalis pedis pulsation was noted before the patient was transferred from the operating table.

Histologic examination of the embolus described above revealed a calcific plaque which, in one region, was continuous with the elastica (Fig. 2). An organizing blood clot was also present. The findings are compatible with those of an embolus consisting of a detached calcific arterial plaque.

The postoperative treatment included heparinization for two days, followed by dicoumarinization for ten days. Papaverine, penicillin, and streptomycin were given intramuscularly. The diabetes was readily controlled with insulin.

The morning following surgery the circulation in the right lower extremity was good, and the veins were full. The patient could now move his toes and foot. The skin temperature on the right side was distinctly higher than on the left limb. Thermocouple skin studies showed an elevation of about two degrees on the right side that persisted for ten days.

The postoperative course was uneventful except for a short febrile reaction associated with a phlebitis at the site of insertion of the intravenous needle, and the development of a hematoma at the operative area. The latter was gradually evacuated, and the wound healed well. Blood presssure was normal during the entire postoperative course.

Further blood chemistry studies showed glucose 142 mg., nonprotein nitrogen 38 mg., cholesterol 210 mg., esters 143.4 mg., total fat 600 mg., lipid phosphorus 8 mg., total protein

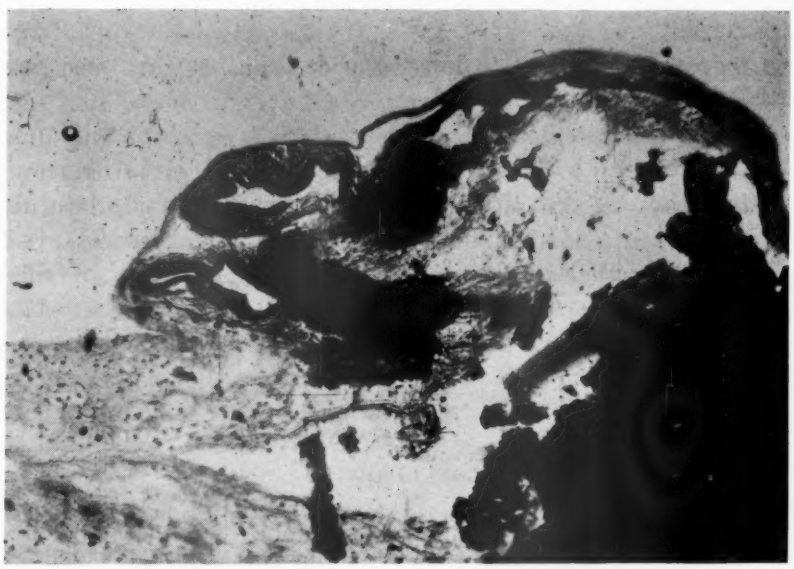

Fig. 2.—Calcific plaque with portion of avulsed arterial wall containing internal elastica.

7.26 Gm., albumin 3.82 Gm., globulin 3.36 Gm., thymol turbidity 4.8 units, cephalin flocculation negative, sodium 136.9 milliequivalents, potassium 5.4 milliequivalents, calcium 4.6 milliequivalents, bilirubin 0.56 mg.

X-ray examinations failed to reveal any calcification of the heart, aorta, or abdominal vessels. There were only faint traces of calcification in the medial lower femoral vessels on the left. No other calcifications were noted.

The patient was ambulant on the seventh day, and discharged eighteen days following admission without any signs of circulatory impairment in the previously affected limb.

COMMENT

The diagnosis of aortic plaque embolism in our patient was based not alone on the presence of certain essential clinical signs, but also on the absence of other significant findings. The clinical picture was that of an acute occlusion at the bifurcation of the common femoral artery. In the absence of clinical

evidence of advanced peripheral artery disease, arterial thrombosis was excluded. Thrombophlebitis with secondary arterial spasm was ruled out by the absence of venous engorgement and the presence of muscular paralysis, and anesthesia. While in the great majority of cases of peripheral embolism a cardiac basis is apparent, the usual findings were not present in our patient. He was not fibrillating and there was no evidences of recent coronary thrombosis, congestive heart failure, valvular heart disease, or patent foramen ovale. Attention was thus directed to the aorta. With no history of trauma or evidence of anuerysm, aortic plaque embolism was suggested as the presumptive diagnosis.

Several interesting questions arose during the management of this vascular emergency. Inhalation anesthesia was chosen in preference to spinal anesthesia. This was logical in view of the good general condition of the patient, and the desire to avoid uncontrollable bleeding that might result from vessel injury by a spinal needle in the presence of a prolonged coagulation time, following the early heparinization.

A blood transfusion helped to lower the coagulation time and limit operative bleeding.

Following the operation, reactive hyperemia was noted on the affected side. This persisted for about ten days, and a temperature elevation could be recorded with thermocouple skin tests. This effect has previously been described.[8]

The heart, thoracic and abdominal aorta, and lower extremity arteries were remarkably free of further calcification on x-ray examination of this diabetic patient.

Although there was early concern about possible complications arising at the site of aortic ulceration, the course was uneventful. This may have been due to the absence of hypertension and the continuous use of anticoagulants.

CONCLUSION

A unique case is presented of avulsion of a large calcific plaque with attached portions of arterial intima that embolized to the femoral artery. The origin was in the proximal artery tree, probably aorta. Successful embolectomy followed a period of observation during which conservative measures were applied.

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ANEURYSM OF THE LEFT GASTRIC ARTERY

A Case Report

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ANEURYSM of the left gastric artery is exceedingly rare. In the last twenty years only one case has been reported in the American literature.[1, 2] This was a cirsoid aneurysmal dilation of a large branch of the left gastric artery within the wall of the stomach. The lesion was 0.5 cm. in diameter. The overlying mucosa was ulcerated and the aneurysm eroded, resulting in a massive gastric hemorrhage. The area was resected and the patient recovered.

The following case differs in that the aneurysm involved the main trunk of the left gastric artery, was considerably larger, and was outside the stomach. The patient had vague digestive symptoms, with persistent occult blood in the stool, and a gastrointestinal x-ray series indicated a filling defect high on the lesser curvature.

Assuming that carcinoma of the stomach was present, laparotomy was done. The exact nature of the disorder was not fully realized until the stomach was explored and the mucosa found to be intact. Then, by placing the fingers in the stomach and the thumb in the lesser omental cavity, it was possible to recognize a pulsatile lesion. It was adherent high on the lesser curvature and was noted to be an aneurysmal dilation of a blood vessel which proved to be the left gastric artery. The aneurysm was resected and the stomach closed. Convalescence was uneventful.

Three months postoperatively, the vague gastrointestinal symptoms had disappeared. Subsequent x-ray studies no longer showed a filling defect in the stomach.

CASE REPORT

D. A., a 68-year-old unemployed white man, was hospitalized on April 24, 1951, with complaints of generalized weakness, upper abdominal distress, and loss of weight. He had not felt well for two years, having been troubled by vague upper abdominal distress. This was neither relieved nor exaggerated by food. Antacids had given no relief. During the past two years there had been a gradual weight loss of 35 pounds. Three days before hospital entry he went to bed because of weakness.

There were no serious illnesses in the past history. Venereal disease was denied. In 1949, during a period of depression, suicide was attempted by discharging a shotgun over the left chest. The resulting injury was a superficial wound over the left anterolateral chest wall with a left hemothorax. He recovered from this injury with no sequelae.

The physical examination revealed a poorly nourished, cachectic, apathetic, elderly man who appeared chronically ill. The temperature was 98.6° F., pulse 88, and blood pressure 180/110. There was moderate redness of the tongue and pharyngeal mucosa. A broad,

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healed, 4 by 2 inch scar was present over the lowermost ribs on the left, in the anterior axillary line. The ribs underlying the scar were irregular to palpation. The lungs were clear, and the heart was not enlarged. The abdomen was scaphoid with no scars. The abdominal aorta could be palpated easily through the abdominal wall. The liver was not felt. There were no abdominal masses or tenderness. Peristalsis was normal. No bruit was heard. Rectal examination revealed poor sphincter tone and a normal prostate. No rectal masses could be palpated. The peripheral vessels were tortuous and hard. The reflexes were physiological and no pathologic reflexes were demonstrated.

The laboratory findings were as follows: red blood cells 4.6 million; hemoglobin 13.7 Gm.; white blood cells 8,600 with normal differential; packed cell volume 42 per cent. The urinalysis showed a slight trace of albumin, negative sugar and acetone, and an occasional coarse and finely granular cast was seen in the sediment. Kahn, Kolmer, and Mazzini tests were negative. The blood urea nitrogen was 44.4 mg. per cent and the total protein 8.3

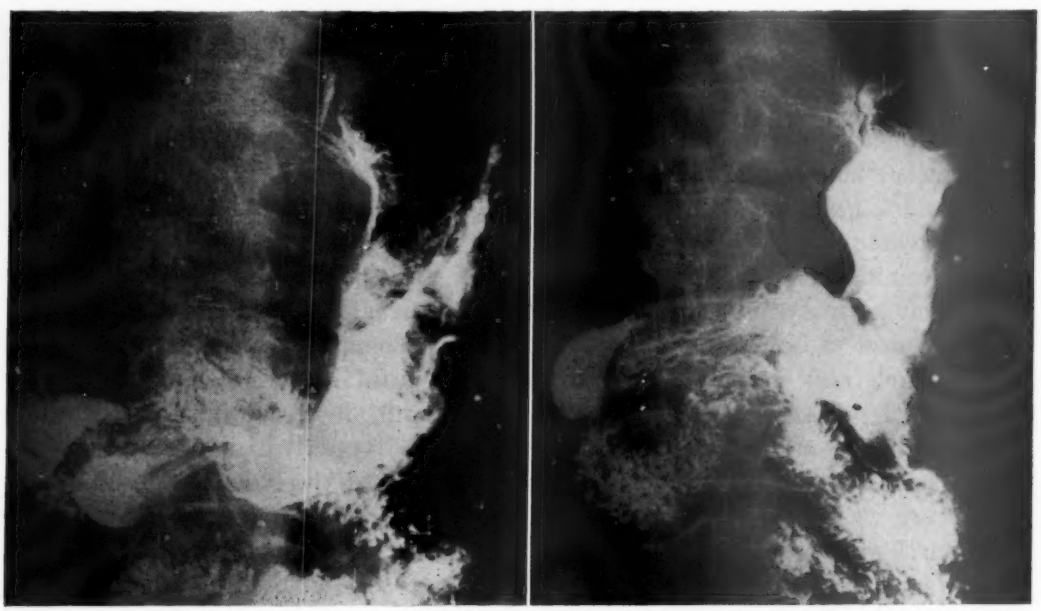

Fig. 1. Fig. 2.

Fig. 1.—Preoperative gastrointestinal series on May 7, 1951. Note the filling defect high on the lesser curvature of the stomach which was present on two examinations.

Fig. 2.—Postoperative gastrointestinal series on Sept. 18, 1951. A peristaltic wave is seen as it passes along the lesser curvature in the region of the former filling defect.

Gm. per cent. Four stool specimens were strongly positive for occult blood, using the benzidine test. Gastric analysis was: fasting HCl zero, total acidity 8. After histamine stimulation the free HCl remained zero; total acidity 18. All specimens except the fasting specimen were positive for occult blood. Three gastric washing specimens for cytologic study all were reported negative for malignant cells.

An x-ray of the chest showed "BB" shot in the lateral left lower chest wall, flattening of the left half of the diaphragm, and a broadened tortuous aorta with increased density and fusiform dilation in the upper descending portion. A barium study of the esophagus demonstrated displacement to the right side, due to the enlarged aorta, but no evidence of intrinsic lesion. Examination of the stomach revealed a constant gross filling defect, quite irregular in outline, in the upper half of the stomach on the lesser curvature. The antrum and duodenal cap were noted to be normal. Carcinoma of the stomach could not be ruled out.

On May 29, 1951, an exploratory laparotomy was carried out through a transverse epigastric incision. A tumor mass 4 cm. in diameter was identified on the lesser curvature of the stomach. It was dark purplish-red in color. Adjacent lesser omentum was considerably thickened. The external appearance of the stomach was grossly normal. Exploration of the upper abdominal cavity otherwise was not remarkable except for an enlarged abdominal aorta. The interior of the stomach was inspected through a longitudinal incision in the anterior portion of the middle third. No gross lesion was noted within the stomach. The mucosa over the lesser curvature was soft and pliable, but the normal rugal pattern was lacking and the mucosa was smooth and thinner than usual over this area. The tumor mass could be palpated through the gastric wall and gave the impression of being fixed to the lesser curvature. The mass was exposed carefully and it soon became apparent that the "tumor" was an aneurysm of the left gastric artery. Branches of the left gastric artery entering and leaving the aneurysmal mass were divided and ligated, and the mass carefully dissected from the lesser curvature.

Pathologic Report.—The opened specimen revealed a saccular aneurysm of the (left gastric) artery, with an internal diameter of 2.5 cm. On microscopic section the wall of the aneurysm was found to be composed of proliferating strands of fibrous tissue relatively scant in collagen. Some of the extracellular material showed fibrinoid necrosis. The adjacent tissues were composed of varying admixtures of fibrin and fatty tissue. The pathologic diagnosis was arterial aneurysm.

The patient's postoperative course was uneventful. The symptoms of epigastric distress disappeared, and his appetite improved. A barium study of the stomach 15 weeks after operation revealed no evidence of extrinsic pressure or of mucosal defect in the stomach.

SUMMARY

1. A case of aneurysm of the left gastric artery is presented. The aneurysm was adherent to the lesser curvature of the stomach and caused signs and symptoms of carcinoma. The lesion produced a filling defect demonstrated by barium x-ray studies. Negative Papanicolaou examinations did not prevent gastric exploration.

2. The aneurysm was resected and the patient's signs and symptoms have disappeared.

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FATAL PULMONARY AIR EMBOLISM FOLLOWING LYSIS OF ADHESIONS

A Case Report

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AIR embolism of the pulmonary type has been described following surgical procedures on the head and neck, uterus, bladder, and prostate. It has also been seen after injection of air for diagnostic or therapeutic procedures, such as tubal insufflation, pneumoperitoneum, pneumothorax, and in cases of criminal abortion. The purpose of this paper is to point out the possibility of this catastrophe following any major surgical procedure and to report a case of air embolism following lysis of adhesions.

CASE REPORT

A 26-year-old Negro man was admitted to Newark City Hospital on June 2, 1950, at 1 P.M. with the diagnosis of acute appendicitis. The patient stated that he had been in good health when he began to experience lower abdominal cramplike pains, increasing in severity, three days prior to admission. He experienced nausea but no vomiting during this time. He had not had a bowel movement since the onset of this pain.

The past history was essentially negative except for a stab wound of the left upper abdomen sustained on Nov. 2, 1949, for which the patient had undergone an exploratory laparotomy at that time. He had an uneventful recovery and had been well up to the present illness.

Physical examination revealed a well-developed Negro man in acute distress with a blood pressure of 120/80, temperature of 99.8° F., pulse 84, and respirations 22. The pertinent physical findings were confined to the abdomen which was slightly distended. There was generalized abdominal tenderness, direct and indirect. Rigidity was present and generalized. No masses were palpable and no bowel sounds were heard on auscultation. There was a left upper healed paramedian incision present. Rectal examination was negative with brown feces on the examining finger.

Laboratory work on admission revealed a cloudy, yellow urine of 1.032 specific gravity with one plus albumin, negative for glucose. There were many leukocytes and a few pus clumps seen on microscopic examination. The white blood count showed 17,000 leukocytes with 92 polynuclears and 8 lymphocytes. The hemoglobin was 15 Gm. (98 per cent), and there were 5,100,000 red blood cells.

A flat plate of the abdomen revealed several distended loops of small bowel with fluid levels present, and an x-ray diagnosis of small bowel obstruction was made.

The patient was prepared for surgery, and an exploratory laparotomy was done at 5:20 P.M. on the day of admission.

Under general anesthesia a lower right paramedian incision was made, and the peritoneal cavity was opened. No free fluid was encountered, but the small bowel appeared to be slightly distended with numerous old adhesions present. These were freed with blunt and sharp dissection and bleeding points ligated. The appendix was located in the right iliac fossa and appeared to be infected, but not sufficiently to account for the physical findings which were present. The appendix was removed with a Merthiolate knife after ligating the meso-appendix. The appendical base was ligated and the stump was inverted with a purse-string suture.

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Further exploration revealed thick adhesions in the right iliac fossa which were partially obstructing the terminal ileum close to the ileocecal valve. These adhesions were dissected free, cut between clamps, and ligated. The ileum was then examined and found to be viable in its full extent. At this point the patient's blood pressure began to fall and respirations became impaired. Other adhesions were palpable in the left upper abdomen under the site of the previous laparotomy scar and were not disturbed. The abdomen was closed in layers using chromic sutures throughout, and the patient expired as the skin sutures were being inserted, despite supportive therapy.

In view of the operative findings and procedure it was felt that this might possibly be another of the so-called "anesthetic deaths." The pathology which was found consisted of partial intestinal obstruction with no impairment of circulation or viability of bowel and was not thought to have been severe enough to cause death. The operative time was one hour and twenty minutes.

An autopsy was done 16 hours after death, and when the abdomen was opened, the small bowel appeared distended with considerable gas and fluid. The serosa was injected and there was no suppurative peritonitis present. There was one area of serosal hemorrhage in the jejunum and adjacent mesentery with ligatures present. Three areas of serosal hemorrhage in the upper ileum and adjacent mesentery where adhesions had been separated were noted. There was one serosal hemorrhagic area at the ileocecal junction and a small hemorrhagic area around the inferior vena cava at that level. There were 2 oz. of blood in the pelvis.

When the chest was opened, the right ventricle appeared flabby and ballooned, and percussed with a resonant sound. The chest was filled with water and the heart pushed back and opened. Large bubbles of air with a little frothy blood escaped. The inferior vena cava was then opened under water and was found to be full of air bubbles.

The endocardium and valves were free and clear in the right heart and there was no hemolysis present.

The autopsy conclusions were sudden death on the operating table due to pulmonary air embolism following lysis of old intestinal adhesions.

Comment.—In this report a massive, fatal, pulmonary air embolism proved by a carefully conducted autopsy is shown. The cause can be traced to the area around the inferior vena cava which revealed hemorrhage. According to Martland, it is not necessary to see a large opening in a vein since pin-point holes may be sufficient to introduce enough air into the venous circulation to initiate a fatal air embolus. This is especially true in dealing with a large vein such as the inferior vena cava.[1] Although most adhesions were freed with sharp dissection between clamps and ligated, it is assumed that some trauma must have been exerted on the inferior vena cava with the occurrence of pin-point holes in this vessel resulting in a fatal air embolus.

CONCLUSION

Pulmonary air embolism, fortunately, is rare following abdominal surgery. As shown by this case, however, the possibility is always present and should be kept in mind by the surgeon. Some of our so-called "anesthetic deaths" may possibly be caused by this phenomenon. Pathologists should be aware of this entity, and a careful examination should be made at the post-mortem table. Prophylaxis can be practiced by careful handling of tissues adjacent to large blood vessels, and strict attention to hemostasis in all abdominal surgical procedures in order to prevent air entering into the venous system.

SUMMARY

1. A case of fatal pulmonary air embolism following abdominal surgery is presented.

2. A carefully conducted autopsy, with the pathologist being aware of this entity, and testing the heart for evidence of air, is necessary in cases of sudden death in surgical procedures.

3. Air embolism, as described, can be prevented with careful handling of tissues and complete hemostasis wherever possible.

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GANGLION OF THE HIP

Case Report

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RECOGNIZED at least since the days of Hippocrates,[1] ganglion is a benign, cystic neoplasm filled with gelatinous material commonly found originating from the joint capsules and tendon sheaths of the peripheral extremities. The cyst may be unilocular or multilocular. Microscopically its wall consists of dense fibrous tissue which shows condensation to form a smooth, white inner surface without special lining cells. Characteristically the cyst wall and adjacent tissues show areas of apparent degeneration filled with myxomatous material.

Several theories have been advanced to explain the etiology of ganglia. The most satisfactory is that published by Ledderhose in 1893[2] and convincingly supported by the American writers Clarke,[3] Carp and Stout,[4] and De Orsay and associates.[5] This describes them as arising by a cystic degeneration of connective tissue. Communication with a joint is considered fortuitous and due to degeneration of the entire thickness of the capsule.

Likewise, several methods of treatment have been advocated. Surgical excision remains the principal, and in this case was the only applicable method.

Gruber[6] reported a ganglion of the shoulder joint. These have been described within tendons,[7] nerves,[8] periosteum,[9] bone,[10] skin, and subcutaneous tissue.[11] The following case is, I believe, the first published of ganglion of the hip joint.

CASE REPORT

History.—D. L., a 42-year-old white store helper and delivery-man, was admitted to Charity Hospital on Sept. 6, 1950, complaining of a mass of three months' duration in his right thigh just below the medial end of Poupart's ligament. This had first been noticed after lifting a heavy object, had grown larger during the last few weeks, and was occasionally painful on straining. His general health was good and past history, system review, and family history were noncontributory.

Physical Examination.—The patient was a well-developed, well-nourished, adult white man in apparent good health. All findings were within normal limits except for a mass in the right thigh in the region of the fossa ovalis approximately 4 by 3 cm. and of unknown depth, but projecting approximately 1 cm. above the surface of the thigh. This was slightly tender and pulsated. No bruit was heard and no impulse was felt on coughing. Blood pressure readings on the four extremities were: right arm—120/80, left arm—126/88, right leg—148/92, left leg—142/92.

Laboratory Data.—Urinalysis, blood counts and chemistries were within normal limits. Kahn and Kolmer tests were negative. Gastric washings were negative for acid-fast bacilli.

Chest X-ray.—Calcification of both hilar regions was seen, without evidence of active vesicular disease.

Electrocardiogram.—Electrocardiogram was within normal limits.

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Surgery.—Surgery was done on Sept. 14, 1950. The preoperative diagnosis was right femoral mass; possible femoral hernia or aneurysm. The postoperative diagnosis was ganglion of the right hip joint. The operation performed was excision of ganglion of the right hip joint.

Fig. 1.

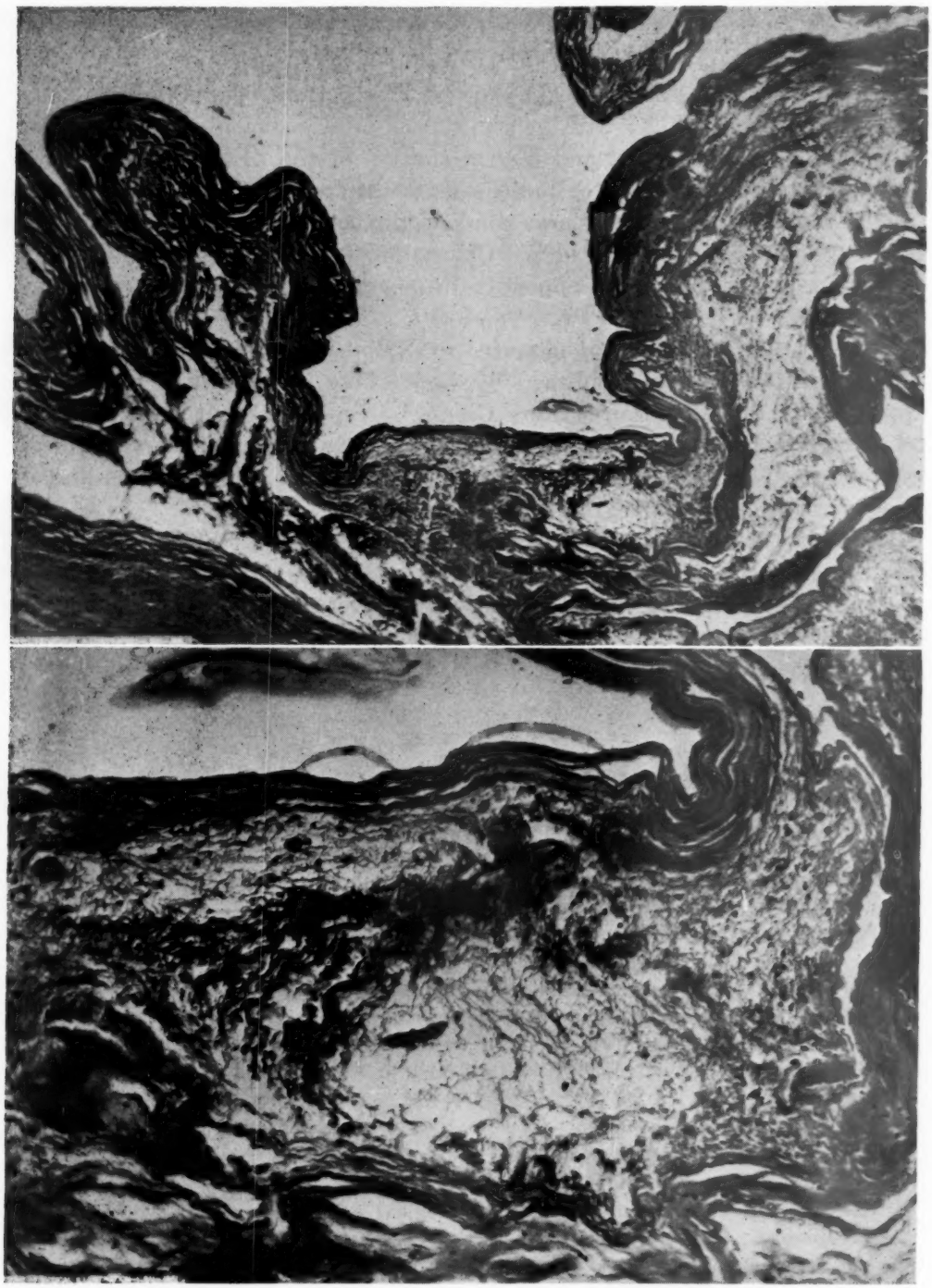

Fig. 2.

Fig. 1.—Low power photomicrographs of specimen.
Fig. 2.—High power photomicrographs of specimen.

With the patient under satisfactory general anesthesia, the abdomen and right thigh were prepared and draped in the usual manner. A 9 cm. incision was made through the skin and subcutaneous tissue 2 cm. above, and parallel to, the right inguinal ligament. All bleeders were caught and tied with No. 80 cotton. The external oblique aponeurosis was split from above down to the external inguinal ring, preserving the nerves. The spermatic cord was freed and the transversalis fascia reflected upward to expose the femoral space. No femoral hernia was present. The femoral artery was isolated and controlled with a small rubber urethral catheter. An 8 cm. incision was then carried through the skin and subcutaneous tissue in an oblique manner across the femoral mass, roughly parallel to and approximately 3 cm. below the right inguinal ligament. All bleeding points were caught and tied with No. 80 cotton. The incision was carried through the deep fascia in the area of the cribriform fascia, the saphenous vein being retracted medially. A fusiform, blue, nonpulsatile mass, approximately 3 by 2 by 2 cm., involving the right femoral artery from the level of the inguinal ligament to approximately 0.5 cm. beyond the deep femoral branch, was encountered. This had the appearance of a femoral aneurysm filled with clotted blood. The deep and superficial branches of the femoral artery were isolated and controlled with small rubber urethral catheters. The posterior surface of the mass was not dissected free lest it represent a femoral aneurysm and such dissection might interrupt collateral vessels. With the femoral artery occluded above, and its branches occluded below, a small opening was made in the wall of the mass lateral to the artery, and clear gelatin-like material exuded revealing a trabeculated, thin-walled sac, smooth and white on its inner surface, filled with gelatinous material, intimately attached to the femoral artery, and extending deeply toward the hip joint. The sac was carefully dissected free and intact from the femoral artery. The deep extension of the structure tapered to a point attached to the capsule of the hip joint over the pubic portion of the rim of the acetabulum. No opening was noted in the capsule, but a pinpoint opening was present at the tip of the deep extension of the sac. Over-all the sac measured approximately 4 by 2.5 by 1 cm. and had the appearance of a ganglion. The lower incision was closed in anatomic layers, using interrupted sutures of quilting cotton. An Anson-McVay type of hernioplasty was performed above as prophylaxis of a femoral hernia in view of the dissection in the region of the femoral space, and the incision closed with interrupted sutures of quilting cotton. Dry dressing was applied and the patient returned to the ward in good condition.

Pathology Report.—Ganglion. (See Figs. 1 and 2.)

Postoperative Course.—Convalescence was uneventful with the patient ambulatory on the first postoperative day and discharged on the fifth (Sept. 19, 1950). Following discharge the patient left this region without reporting for follow-up or leaving a forwarding address.

SUMMARY

A proved case of ganglion of the hip joint simulating femoral hernia or aneurysm and treated by excision has been presented. This is believed to be the first published case of ganglion of the hip.

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Editorial

German Interns in America

ONE of the most encouraging experiments in the exchange of students from abroad is a little known program now under way in New Jersey hospitals. Twenty-seven German medical graduates are serving for one year as interns in hospitals scattered across the state from Hackensack to Atlantic City. They were brought here, not by the State Department nor by one of the large foundations, but by a practicing physician in Atlantic City, Dr. Hilton Read and his wife, Kathryn, who went to Germany last summer to choose the candidates and arrange for their transportation. It was their purpose to promote better understanding between the medical professions of the two countries.

Recently in Atlantic City this group of interns gathered at the Hotel Dennis to listen to as stiff a schedule of speeches as ever weighted a "Universitat" curriculum—thirteen speeches in twenty-four hours. The title was vague —"The Dynamics of Democracy"—and drew no crowds of busy New Jersey physicians, nor did the meeting draw fitting comment from the national press. Yet this gathering was as brilliant a sample of American thought at its best as many observers had seen.

Ten guest speakers developed ten different subjects; only one, Dr. Howard Rusk, was a physician. Yet somehow there was a "meeting of the minds," and out of the whole came a composite picture of America, of a vast continent overrun by a variety of races, cultures, and classes which could never merge completely in the melting pot as in many other nations, but must learn to live together by adjusting their differences through compromise and conciliation. How this process of hammering out differences takes place over the conference tables of unions, in the courtrooms of the law, and in our social milieu is the thing that baffles many foreign observers accustomed to an orderly inheritance. Most difficult for them to understand is our international leadership, which we have developed only in the short space of seven years and which is still characterized by the disputatiousness of our domestic dealings, and the ineptness of our inexperience.

Medicine must lead in the effort to develop understanding between nations. Howard Rusk pointed out that medicine is probably the most international of the professions; it has always been above race and creed, and the growth of medical knowledge has arisen as a composite of the contributions of all nations.

The gaps in international understanding are great but not insurmountable —bad news is too often played up at the expense of good news. Clarence Pickett of the American Friend's Service Committee, who for many years has sat across the conference table with teams from many countries and is now on

the sidelines at the United Nations Assembly, cited many areas of agreement that are now being worked out. He finds the Russians far from hopeless in the settlement of disputes and believes that by concentrating on the small problems that can now be solved we may build up attitudes of compromise that will carry over into the larger problems whose solution is so necessary.

The tone of the Atlantic City meeting was one of thoughtfulness and humility. No one suggested that our brand of democracy should be exported to countries with a different ethnic and cultural heritage.

Three exchange students reported on their experiences in this country, noting particularly the greater responsibility allowed to interns in our hospitals, and commenting in some surprise on the friendly reception accorded them by persons outside the hospital staffs.

Dr. Hilton Read's experiment is a reminder that a "Weltanschauung" is important to the medical profession, as it is to all Americans, and that it may be achieved by private individuals without great fanfare or large outlays of money.

—Barbara K. Fitts.

Recent Advances in Surgery

Conducted by Alfred Blalock, M.D.

SURGERY OF TUMORS AND HYPERFUNCTIONING STATES OF THE ADRENAL GLANDS

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THE striking and almost spectacular clinical picture which so frequently accompanies derangements of the adrenal gland has made these conditions, in spite of their infrequency, a most interesting subject for study. With the better understanding of the functions of the adrenal gland it has become possible, in many instances, to correlate the clinical manifestations of the adrenal disease with the altered secretion of one or more of the multiple hormones secreted by the suprarenal glands. This knowledge has also made possible a more rational approach to the treatment of these conditions. The purpose of this presentation is to present examples of the more common derangements of the adrenal gland seen and treated at the University Hospitals from 1941 to 1951.

As a background for this clinical presentation, a brief review of the embryology, anatomy, and physiology of the adrenal glands is in order.

EMBRYOLOGY

The adrenal is composed of two structurally different parts having different embryologic origins and entirely distinct functions.[1]

The medullary portion is derived from the embryonic neural crest and thus has a common origin with sympathetic ganglia. As their development proceeds, the primitive cells differentiate themselves further into nerve cells and chromaffin cells, the latter being distinguished by their granules which take on a characteristic brown color with chromic acid stains.

The cortex arises as a group of cells from the celomic epithelium next to the mesonephros. The germinal epithelium from which the sex glands arise also originates from the celomic epithelium in this region. The cortex comes to surround the highly vascularized medulla. The descent of these two components to the definitive position above the kidney is a complicated one and aberrant adrenal tissue may be found in various positions. These accessory adrenal cortical bodies (Marchand bodies) may be found along the retroperitoneal tissues of the paracolic gutters, in the broad ligaments, the ovaries,

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and the testes. It is important to remember these anomalies because tumors arising in these adrenal rests have occurred and have produced syndromes similar to neoplasms arising within the adrenal gland.

The adrenal, relative to body size, is largest at birth, with the major portion of the gland being composed of adrenal cortex. The latter is divided into a large inner androgenic or "X" zone and a thin outer layer of cortical cells similar to that observed in later life. The cells of the androgenic zone are fuchsinophilous and are rarely found in the adrenals of older children and adults except in pathologic states. The reduction in size of the adrenal cortex after birth takes place during the first few months and is due essentially to the rapid degeneration of the "X" zone. The true cortex is left behind and continues to grow and develop. The growth becomes considerably accelerated just before and during puberty but continues at a much slower rate until middle life. The adrenal cortical cells grow continuously from without in, that is, its cells arise from the spindle-shaped cells under the fibrous capsule and pass inward to form the three zones: the zona glomerulosa, the zona fasciculata, and the zona reticularis.[2] During this process the cells elaborate, accumulate, and discharge lipoid sterols into the capillaries; then degenerating, they are removed by microphages and microphages near the medulla.

PHYSIOLOGY

Adrenal Medulla.—Adrenalin is apparently formed from the chromaffin cells whose granules will stain blue with ferric chloride, a reaction characterizing adrenalin. It was pointed out by Cannon[3] that the release of adrenalin is largely an emergency function and effects are directed in a manner to permit an animal to meet the emergency. As is well known, adrenalin causes vascular constriction, increased contractility of the heart, dilatation of the coronaries, relaxation of the smooth muscles of the bronchi, and increase in blood sugar by conversion of muscle and liver glycogen into blood glucose. As important as all these functions appear to be, the adrenal medulla is not absolutely essential for life.

Adrenal Cortex.[1, 4-8]—There is considerable controversy as to whether the adrenal cortex elaborates only one hormone which has multiple functions depending on its metabolism, or whether there are a number of hormones with different functions. In spite of this controversy it is generally agreed that the adrenal cortex manifests the following distinct metabolic activities: (1) maintenance of the electrolyte and water balance, (2) influence on carbohydrate metabolism, and (3) augmentation of protein anabolism.

1. *Electrolyte and water balance:* The steroids concerned with the regulation of electrolyte and water balance are corticosterones in which the O or OH group attached to C_{11} is absent. The compound in this group which has been studied most intensively is 11-desoxycorticosterone. Its administration causes retention of sodium, chloride, and water, and increases the urinary

excretion of potassium and phosphorus. In adrenal insufficiency there is a marked decrease in the sodium and chloride ions, and sharp elevation of potassium ions. The plasma volume decreases and depression of kidney function results in retention of blood urea nitrogen. Desoxycorticosterone is capable of correcting these abnormalities.

2. *Hormones influencing carbohydrate metabolism:* These compounds are corticosterones with an O or OH group attached to C_{11}. Four known examples are corticosterone, 11-dehydrocorticosterone (Kendall's compound A), 17-hydroxycorticosterone (compound F) and 17-hydroxy-11-dehydrocorticosterone (compound E). These hormones are gluconeogenic. They promote deamination of amino acids and their conversion to carbohydrate. Recently, compound E, or cortisone, has been shown to have a dramatic effect on rheumatoid arthritis, acute rheumatic fever, asthma, hay fever, serum sickness, lupus erythematosus, periarteritis nodosa and a host of other conditions. Unfortunately, in practically all cases the results are temporary, and serious side effects have been reported attending its use.

3. *Augmentation of protein anabolism:* A number of steroids having the chemical structures of androgens have been isolated from the adrenal cortex and from the urine of normal or castrate men and women. The best known is androsterone. These compounds are apparently responsible for the marked degree of virilization and rapidity of growth and marked muscular development seen in hyperadrenocorticism. There is also convincing evidence that adrenal androgens are responsible for the growth of sexual hair, labia majora, and clitoris and for the appearance of seborrhea and acne in the sexual development of the normal female. Excessive elaboration of these compounds exerts its influence on these "target structures" and is responsible for the clinical picture of hyperadrenocorticism in the female.

Progesterones and estrogens have also been isolated from the adrenals and urine of both sexes. The latter hormone in excess may be responsible for the gynecomastia seen with certain feminizing tumors of the adrenal males.

The General Adaptation Syndrome.—As discussed above the adrenal medulla elaborates epinephrine which aids the organism in meeting acute stresses. Selye[9] has studied the role of the adrenal cortex in a variety of stresses such as burns, trauma, fatigue, cold, prolonged starvation, infections, etc., and these stimuli apparently cause an outpouring of cortical hormones, followed by hypertrophy of the adrenal cortex. The metabolic activity of these hormones results in an increased gluconeogenesis, atrophy of the thymus and lymphoid tissues, increased polymorphonuclear count, and decreased number of lymphocytes and eosinophils. Uric acid is increased in the blood and urine. This response on the part of the adrenal cortex is mediated through the pituitary by the production of ACTH.

DISEASES OF THE ADRENAL GLAND

Tumors of the Adrenal Medulla

I. *Neuroblastoma.*—These tumors arise from the nerve cells of the medulla.[10] The more primitive the cell from which the neoplasm arises, the more malignant is its nature. Depending upon the histologic appearance, the neuroblastoma sympatheticum may thus be differentiated into the extremely malignant sympathogonioma, the malignant neuroblastoma, and the relatively benign ganglioneuroma. Of these three tumors, the neuroblastoma is by far the most common and is the most common neoplasm of the abdominal cavity in children under the age of four.[11]

In the very early case the tumor may be small and encapsulated, but invasion of adjacent organs such as the kidneys, mesentery, vertebrae, pancreas, etc., occurs with unhappy rapidity. On cross-section, the tumor is usually soft and spongy and in many instances there is considerable necrosis. Metastases tend to occur readily by both the lymphatic and blood streams and are only rarely limited to regional involvement of the lymph nodes. More frequently, metastases in the lung, liver, brain, and skeletal system occur. The differentiation into the Pepper syndrome, in which metastases to the liver occur, and the Hutchinson syndrome, in which metastases to the skull orbit predominate is no longer tenable because the pathology in either instance is the same and clinical manifestations are dependent upon which part of the body is invaded by the tumor. Histologically, the neoplasm is a highly cellular tumor with considerable pleomorphism, frequent mitoses, and a tendency to rosette formation. Neurofibrils are usually present and are demonstrated by a phosphotungstic acid hematoxylin stain. The tumors in which the cells show no tendencies for rosette formation and neurofibrils cannot be identified are sympathogoniomas and are extremely malignant. When the cell differentiation is in the larger ganglion cells, the neoplasm is a ganglioneuroma and is relatively benign.

Although neuroblastomas arise primarily within the adrenal gland it must be remembered that they may arise from other sympathetic nerve tissues along the retroperitoneal, retropleural, or even cervical areas. The organ of Zuckerkandl at the bifurcation of the aorta may also give rise to this neoplasm.

Clinically, the neoplasm has no specific clinical picture and the initial complaint is usually related to abdominal swelling associated with increasing fatigue, loss of appetite, and pain suggestive of neoplastic involvement of the retroperitoneal nerves or invasion and obstruction of the kidney pelves, or ureters. Unfortunately, very frequently metastases are the first findings to suggest the diagnosis of neuroblastoma. Treatment ideally consists of excision of the mass, but rarely is this possible. The main form of therapy in this situation is roentgen therapy and this should be given even where there are evidences of widespread metastases. Radiation therapy should, therefore, be given to the mass within the abdomen as well as the sites where metastases have appeared. Although the prognosis is poor, Farber and his group at the

Boston Children's Hospital have seven patients out of a series of thirty-two histologically verified cases who have survived two or more years following either complete surgical removal, or, when that was not feasible, the use of x-ray therapy. Two of the seven patients had liver metastases.[11]

REPRESENTATIVE CASE STUDY.—W. J. C., a 3-year-old boy, was apparently well until the middle of June, 1941, at which time he developed listlessness and mild dysuria. Two weeks later there was weakness of the right lower extremity and at that time his hemoglobin was 7.5 Gm. per cent. On Aug. 20, 1941, he developed an exophthalmus of the left eye, and x-rays

Fig. 1.—A 3-year-old boy with neuroblastoma. Symptoms present only three months. Note exophthalmus and bulging of left temporal area. Large nodular mass in right upper quadrant of abdomen outlined by skin markings.

From McQuarrie: Experiments of Nature and Other Essays, University of Kansas Press.

of the chest showed widening of the mediastinal shadow. He was admitted to University Hospitals on Sept. 11, 1941, at which time examination showed him to be undernourished, anemic, and obviously ill. (Fig. 1.) Bilateral exophthalmus, discoloration of the eye lids, and bulging of the left temporal area were the most striking features. In the abdomen there was a large, hard, nodular, and tender mass, filling the right upper quadrant. Unfortunately, no x-ray

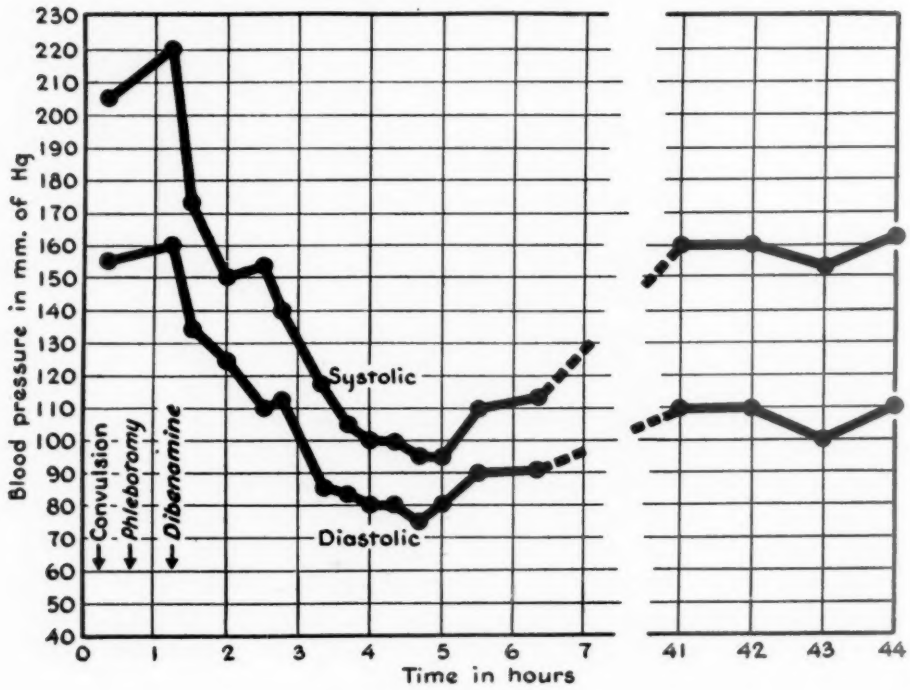
therapy was undertaken, but from the advanced stages of development it is questionable whether anything other than a short period of palliation could have been brought about. He died on Oct. 25, 1941, approximately four months from the onset of the symptoms. Autopsy revealed the presence of a large neuroblastoma involving the right suprarenal gland with metastases to the liver, mediastinum, skull bones, and osseous skeleton.

Comment: The history here typifies the usual clinical picture of the vagueness of the onset. Metastases occurred early and formed the prominent features of the case. As stated previously, neuroblastoma is the most frequent intra-abdominal neoplasm in children under four and if a mass is suspected, even though special examinations fail to confirm its presence, an aggressive attitude toward exploration of the abdomen should be carried out with the hope that these lesions may be uncovered early so that the prognosis may, thereby, be improved.

II. *Pheochromocytoma.*—This neoplasm, arising from the chromaffin cells of the adrenal medulla, is being recognized with increasing frequency as a cause of arterial hypertension. Newer diagnostic drugs have aided in differentiating patients with hypertension due to pheochromocytoma from those with hypertension due to other causes. The disease is rare in children, only eight patients under thirteen years of age having been described.[12] The symptoms that characterize pheochromocytoma are primarily those due to overproduction and release into the blood stream of epinephrine-like substances. Characteristically, one sees paroxysmal arterial hypertension, tachycardia, or tremor, nausea, vomiting, and sweating. The intermittent nature of attacks has been emphasized in the past, but Green[13] has pointed out that chronic hypertension was present in thirty-seven of fifty-one cases he reviewed. Pheochromocytoma must be differentiated from other entities which give rise to hypertension, namely, renal disease, coarctation of the aorta, acrodynia, lead poisoning, Cushing's syndrome, hyperthyroidism, tumors of the hypothalamus, and essential hypertension. Roth and Kvale[14] have advocated the use of histamine to differentiate pheochromocytoma from other causes of persistent hypertension, because this drug precipitates the paroxysmal attack associated with pheochromocytoma. This test may be dangerous and is consequently not being used routinely. The use of a sympatholytic drug such as Dibenamine[15] and benzodioxane[16] has been advocated and is a safer approach to the diagnosis, for instead of precipitating an attack it actually inhibits the action of adrenalin. This results in a fall in blood pressure which is a more desirable effect. The following case report of a patient seen at University Hospitals outlines the problems of diagnosis as well as therapy.

J. D., a girl eleven years of age, was admitted to University Hospitals on May 23, 1948, with a history of having developed a "flulike" illness consisting of fever and anorexia eight days prior to admission. Four days later a diagnosis of acute pharyngitis and cervical adenitis was made and therapy instituted. On the morning of the day of admission she developed headache and vomiting which persisted until the onset of convulsive seizures three hours prior to admission to the hospital. Physical examination on entering the hospital revealed a thin, well-developed, comatose and mildly cyanotic child, perspiring profusely and having repeated convulsions. Seizures were controlled by Sodium Amytal given intravenously. Her temperature was 104° F., pulse rate 176, blood pressure 174/100 mm. Hg. A catheterized

Fig. 2.



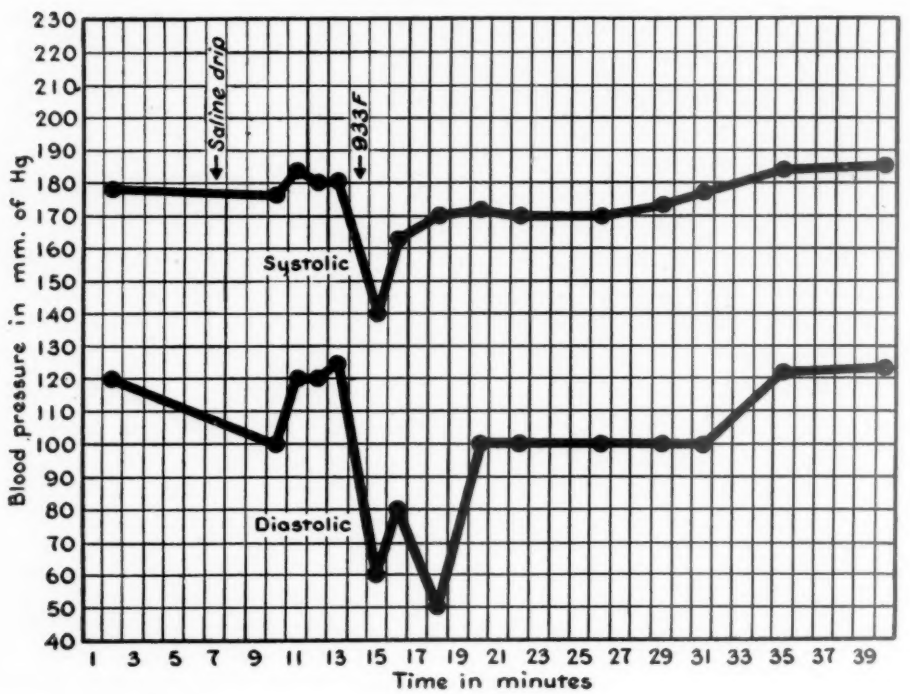


Fig. 3.

Fig. 2.—Effect of Dibenamine (6 mg. per kilogram of body weight) on hypertension due to pheochromocytoma. Note the marked and prolonged drop in pressure.

Fig. 3.—Effect of benzodioxane on hypertension due to pheochromocytoma. A significant drop in blood pressure occurs but lasts only a short time.

urine specimen showed 2 plus albumin, occasional casts and red blood cells. The presumptive diagnosis was acute glomerulonephritis and the patient was given magnesium sulfate intramuscularly in a 25 per cent solution (0.2 c.c. per kilogram of body weight). Within two hours the systolic blood pressure had fallen to 150 mm. Hg systolic, but the diastolic blood pressure remained elevated at 120 mm. Hg. The patient regained consciousness but the blood pressure continued to be elevated consistently above 150/120 mm. Hg. On the third hospital day the blood pressure rose to 210/150 mm. Hg and persisted at extremely high levels for the next several days in spite of intensive magnesium sulfate therapy.

Because of persistent hypertension the possibility of pheochromocytoma was strongly considered. The mother was questioned again in more detail regarding the past history and she stated that the patient had had intermittent bouts of headaches and vomiting beginning at two years of age.

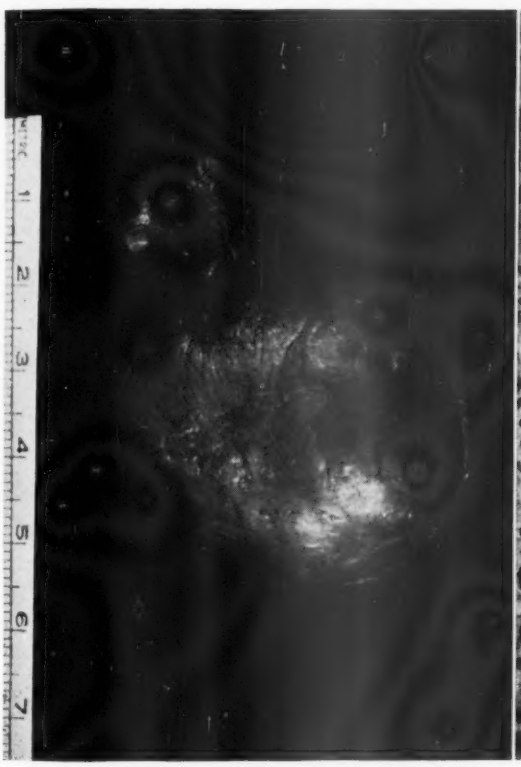


Fig. 4.

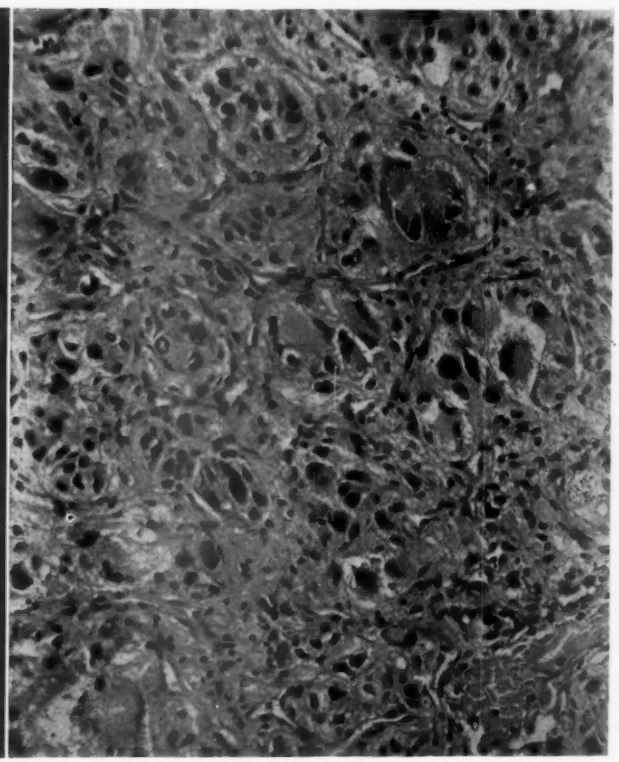


Fig. 5.

Fig. 4.—Pheochromocytoma of the right adrenal gland. This tumor was well encapsulated but had no definite pedicle.

Fig. 5.—Microscopic section of removed pheochromocytoma. Note alveolar patterns of cells. Giant cells are present and some nuclei show mitoses.

Dibenamine, sympatholytic drug, was made available to us* and was given in doses of 6 mg. per kilogram of body weight with a response as shown in Fig. 2. The blood pressure dropped from 206/154 to 94/74 during a period of approximately 4½ hours after the administration of Dibenamine. The depression of blood pressure lasted 41 hours before stabilizing at 160/110. Benzodioxane compound 933F,† another epinephrine-inhibiting drug, was given approximately one week later and again a drop in blood pressure occurred, lasting however, only approximately five minutes. (Fig. 3.) Intravenous pyelograms revealed no tumor masses in the adrenal region but in view of the response to the antiadrenergic drugs,

*Received from Dr. M. Nickerson, University of Utah.
†Received from Dr. C. Harrison Snyder, University of Utah.

pheochromocytoma was considered the most likely diagnosis and surgical exploration was carried out on June 2, 1948.

Preoperatively, Dibenamine was given in an effort to prevent an excessive rise in blood pressure that might occur from manipulation of the tumor. Under Pentothal Sodium anesthesia the abdomen was explored through an upper right rectus incision. The left adrenal gland was found to be normal, but a mass involving the right adrenal gland was encountered. Upon manipulation of this tumor the blood pressure did not become elevated. Shortly before the removal of the tumor the blood pressure was 150/90 mm. Hg. The tumor was easily enucleated but following its removal the blood pressure fell precipitously to a level too low to measure and the pulse became thready. One c.c. of 1:1000 epinephrine solution and 10 c.c. of adrenal cortex extract were given intravenously but no blood pressure readings were obtainable and cardiac arrest occurred. Repeated injections of epinephrine both intravenously as well as direct introduction of the drug into the myocardium and transfusion of blood failed to bring about any favorable response. The patient received 50 c.c. of a 1:1000 solution of adrenalin over a period of fifteen minutes without any appreciable effect on the pulse or blood pressure. Cardiac massage through a transthoracic incision was started but although the myocardium responded briefly after two hours of manipulation no further contractions could be obtained and the patient was declared dead.

Grossly, the tumor removed weighed 22 Gm. and measured 3.5 by 2.5 c.c. (Fig. 4). It was a well circumscribed, encapsulated, gray-brown tumor of fairly soft consistency. Microscopically the tumor was composed of polymorphocellular cells arranged in rounded clusters and alveoli of rather small size. There were a number of giant cells and some nuclei showed mitoses. Uniformly distributed throughout the sections were clusters of fine brown pigment. (Fig. 5.)

Comment: From the standpoint of diagnosis the possibility of pheochromocytoma should always be considered in patients with hypertension. The availability of benzodioxane and Dibenamine permits a ready differential diagnosis between this tumor and other causes of hypertension. It is not entirely specific, however, for recently Calkins and associates[17] reported a patient giving a positive response to 933F who was found to have a large-cell neuroblastoma, and in some cases of pheochromocytoma the results of the benzodioxane may be atypical or negative.

From the surgical point of view, the major problems in handling cases of pheochromocytoma are the marked elevation of blood pressure associated with manipulation of the tumor during operation and the precipitious fall of blood pressure following removal of the tumor. In the case reported the Dibenamine given did prevent the excessive rise in blood pressure associated with manipulation of the tumor but it was most likely the cause of the failure of response by the patient to the adrenalin after the removal of the tumor. Thus its use is unwise and in its place some shorter acting adrenolytic substance such as benzodioxane is more ideal.

There is no unanimity concerning the exact mechanism of the fall of blood pressure and consequently, there is a variety of opinion as to how to counteract it.

The following points are important in carrying the patient safely through the operation.

1. Before the operation is begun an intravenous infusion should be started with a large-bore needle so that if the need for rapid infusion arises, it can be carried out. Epinephrine in 1:100,000 solution, whole blood, and adrenal cortical extract should be available, in case they are needed.

2. Anesthetic agents that profoundly influence blood pressure should be avoided—Pentothal Sodium-curare solution is an excellent choice in this regard.

3. Adequate exposure of the adrenal should be carried out so that manipulation is reduced to a minimum and the vascular supply to the gland is readily available for clamping. The transabdominal approach is preferable to others because, in addition to ready exposure, it permits examination of (1) the other adrenal, and (2) the peritoneal cavity for ectopic tumors. It has been shown that pheochromocytomas may be multiple with simultaneous tumors in both adrenals.[18]

4. If at all possible, before the tumor is removed the pedicle should be clamped and released repeatedly with the period of occlusion gradually increased until the blood presssure remains stable for a period of ten minutes of pedicle clamping. When this occurs it means the vascular system has made its adjustment to the withdrawal of the large amount of vasodepressor substances elaborated in the adrenal tumor.

5. To counteract the excessive hypertension associated with the manipulation of the tumor, benzodioxane may be given intravenously or the patient may be given amyl nitrite by inhalation.

6. If a precipitous drop in blood pressure occurs, the epinephrine solution and whole blood should be given quickly and in quantities sufficient to bring the blood pressure back to normal levels. Adrenal cortical extract in doses of 10 c.c. intravenously should also be given. Postoperatively the patient should be watched carefully for delayed drops of blood pressure and in some patients it may be necessary to utilize a continuous infusion of 1:100,000 adrenalin or noradrenalin (an isomer of adrenalin) for several days at a fast enough rate to maintain normotension.

The mortality rate continues, however, to be high and the longer the duration of the disease the higher the mortality. In children, to date, the death rate attending operation has been very high—58 per cent.

Diseases of the Adrenal Cortex

I. *Hyperadrenocorticism.*—Because of the multiplicity of steroids secreted in the adrenal cortex it is not surprising that neoplasms or hyperplasia of the gland may give rise to a wide variety of symptoms attributable to an excess of one or of a number of these different hormones. However, nearly all cases of hyperadrenocorticism may be divided on the basis of their predominating metabolic manifestations into two groups (1) adrenogenital syndrome and (2) Cushing's syndrome.

A. *Adrenogenital syndrome:* The manifestations of adrenocortical hyperplasia depend upon the sex of the patient, and on whether hormonal dysfunction began in early embryonic life or after the intrauterine differentiation of the sex organs had been completed.

1. Congenital Adrenal Hyperplasia in the Female Sex (Female Pseudohermaphrodism).—This is the most common adrenal disorder encountered in childhood. At birth children with this disorder have an enlarged clitoris resembling hypospadias and composed only of corpora cavernosa. It is

bound ventrally by fibrous cords, extending backward from the under surface. The labia majora are hypertrophied, while the labia minora are underdeveloped or represented only by fibrous cords. Between the labia there is a single opening which is the urogenital sinus, usually with a small orifice resembling the urethral meatus. Occasionally the urogenital sinus opens to a large funnellike orifice resembling a small vagina rather than a urethra and rarely the communication between the vagina and urethra is not patent, although the anatomic relationships are otherwise the same. These patients have ovaries and uterus and normally developed Fallopian tubes. From birth on, these infants continue to show evidence of increased secretions of androgens. Somatic growth, sexual hair growth, muscular development, and epiphyseal ossification becomes far advanced for the age of the patient. Acne develops early. Hypertrophy of the clitoris continues and there may be almost constant erections. The voice becomes deep and excretion of the 17-ketosteroids is always increased in relation to the patient's age. The child's general appearance may be quite feminine in early childhood but, as puberty is reached, the breasts do not develop, epiphysial fusion occurs early. These individuals become adults with short, stocky, muscular bodies with coarse, dark hair on the thighs, legs, abdomen, and face.

PATHOLOGY: Both adrenals are usually enlarged to about 1½ to 3 times the normal size. Occasionally, the hyperplasia appears to be primarily unilateral. Microscopically, the glands are composed principally of large polyhedral granular cells staining deeply with fuchsin and resembling those of the fetal androgenic or "X" zone. The other zones of the cortex are diminished or absent.

DIFFERENTIAL DIAGNOSIS: The conditions from which female pseudohermaphrodism must be distinguished are: (1) intersexuality, (2) postnatal virilization, and (3) sexual precocity of the iso-sexual type.

Intersexuality or Hermaphrodism: This may present a real problem in the differential diagnosis because some patients with intersexuality may have a urogenital sinus, vagina, uterus, and Fallopian tubes but instead of ovaries they have testes or ova-testes. The finding of a low 17-ketosteroid is suggestive of intersexuality whereas a high excretion is characteristic of congenital adrenal hyperplasia. Sexual hair and other secondary male characteristics develop during childhood in pseudohermaphrodism of adrenal origin, but do not appear until the usual age of puberty in intersexuality. However, laparotomy and biopsy may be necessary to differentiate between the two.

Postnatal Virilization: Virilization due to adrenal tumor or hyperplasia developing postnatally is distinguished by the fact that the patients have a normal vulvar configuration and separate urethra and vagina.

Precocious Iso-sexuality: Sexual development along a normal female pattern is not liable to be confused with adrenal hyperplasia. The genitals are normal; the breasts, labia, and vagina develop almost simultaneous with the appearance of sexual hair.

TREATMENT: Treatment of pseudohermaphrodism is a complex and difficult task. Genetically these patients are females but because of the excessive secretion of androgen, the external manifestations of sex are predominately in the male direction. Unfortunately, the removal of one adrenal gland or portions of both adrenal glands has resulted in no significant change in the clinical course. Until recently there has been no good way of depressing the excessive androgenic function of adrenal glands but Wilkins and associates[19] have called attention recently to the fact that cortisone may possibly do this. It is worthy of trial to prevent progressive virilization in selected cases under most careful observation.

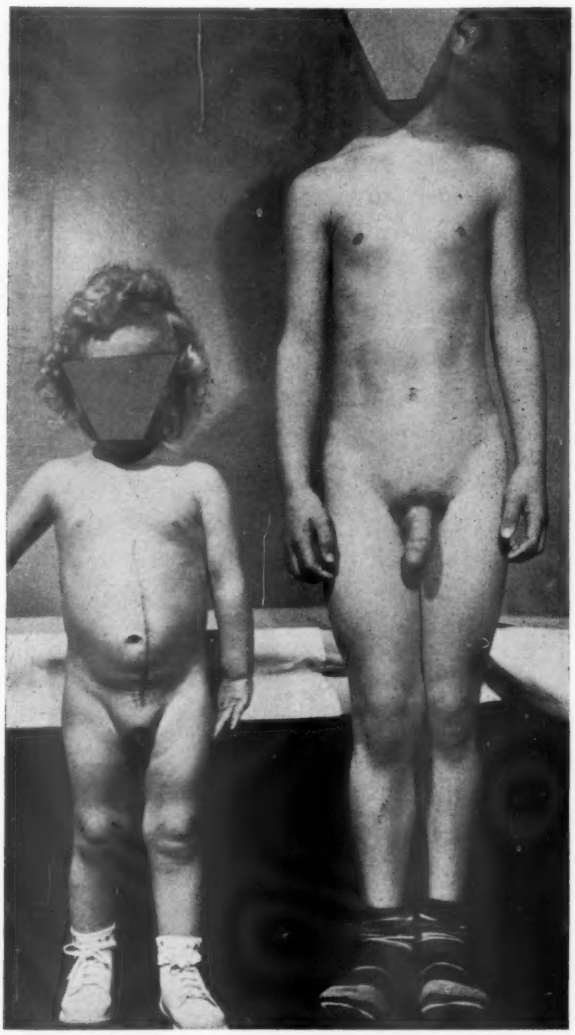


Fig. 6.—Siblings showing congenital hyperplasia of the adrenals. A cousin also had this condition. The girl was 16 months of age and the boy 4 years of age. Note abundant pubic hair and enlarged penis of the brother. The testes, however, are small.

When the diagnosis has been made early in the child's life, since the genetic pattern is a female one, most physicians feel that the child should be

brought up as a girl. To this end the clitoris may be amputated, and at the time of puberty attempts may be made at increasing the femininity of the patient by the use of estrogenic hormones. In later childhood or in adolescence, plastic procedures can be performed to construct a separate urethra and vagina.

In those cases where the child has been reared a boy, it may be best to continue with this plan because of the excessive androgenic activity at the time of puberty. At laparotomy the tubes and ovaries can be removed although this is probably unnecessary in view of their atrophic condition. The chordee can be corrected and plastic procedures to form a penile urethra may be carried out. It may be necessary to give additional testosterone at puberty to aid virilization of the patient at this time. When one is faced with the choice of plans in early childhood the best pathway may be to permit the child to develop as a boy.

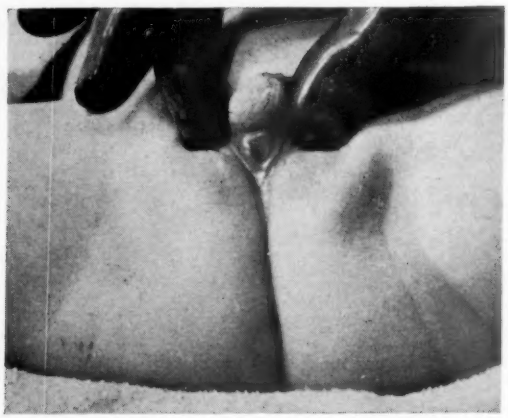


Fig. 7.—Photograph showing clearly the enlarged clitoris and urogenital sinus of typical congenital adrenal hyperplasia in a female child.

CASE REPORT (congenital adrenal hyperplasia in the female).—P. M., a 16-month-old girl, was admitted to the University Hospitals because the parents noted growth of public hair and enlargement of the clitoris soon after birth. The child's health was good and the rate of development was normal. She had a brother four years of age who also showed hyperadrenocorticism (Fig. 6).

Physical examination revealed a well-developed and well-nourished white child who appeared well and healthy. There were no masses in the abdomen. The external genitalia showed fine pubic hair, a hypertrophied clitoris, urogenital sinus, i.e., a common opening for meatus urethra and vagina (Fig. 7), scrotalized labia majora and small fused labia minora. Rectal examination revealed a normal infantile uterus.

Laboratory tests showed a hemoglobin of 10.6 Gm. per cent; leukocyte 10,500, with a normal differential. The blood urea nitrogen was 10 mg. per cent, CO_2 combining power 21 meq. per liter and chloride 99 meq. per liter. The serum sodium and potassium were respectively 148 and 5.4 meq. per liter. The glucose tolerance and eosinophil response to ACTH were normal, indicating good adrenal reserve. Unfortunately, it was not possible to get a 17-ketosteroid level in the urine preoperatively.

In order to (1) rule out an adrenal cortical tumor, and (2) determine the sex of the child a laparotomy through a long left paramedian incision was carried out using Pentothal Sodium-curare anesthesia with intratracheal oxygen. The adrenals were only slightly enlarged and no ectopic adrenal tissue was found. In the pelvis a uterus of normal infantile

size, with tubes and ovaries, was found. The right ovary had a small cyst about 4 mm. in diameter. Biopsies of both adrenals and ovaries were taken and the peritoneum closed in layers using interrupted 000 silk.

Histologic examination of the adrenal biopsies showed normal adrenal by the hematoxylin eosin stain. Ponceau-fuchsin stains showed a small number of fuchsinophilic cells. The ovaries showed numerous graafian follicles of varying sizes with numerous ova in the cortex (Fig. 8).

Postoperatively, apart from some atelectasis of the right upper lobe, the patient did nicely.

Comment: Congenital hyperplasia of adrenals may occur in siblings as this case illustrates. In certain families, two to five children may show this disorder while other children do not. In spite of the high familial incidence, occurrence in more than one generation has not appeared in the literature.[4]

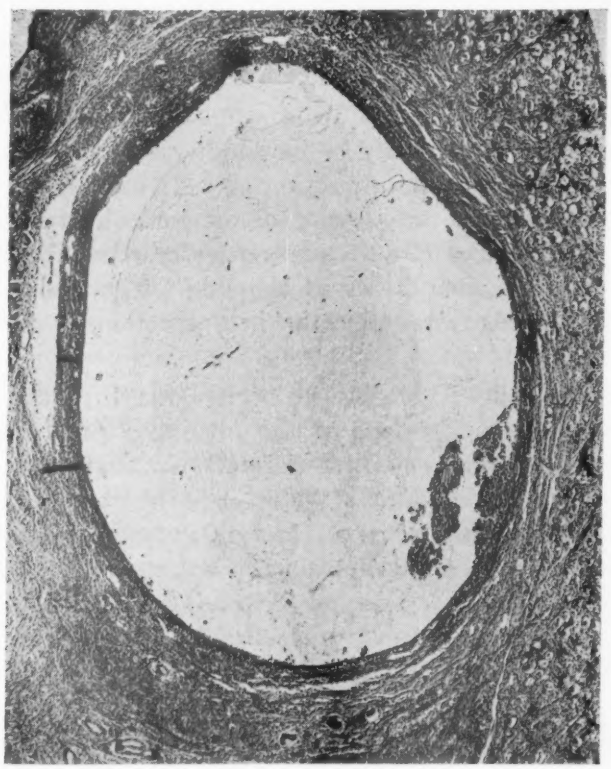


Fig. 8.—Microscopic section of biopsy of the ovary of 16-month-old girl with congenital hyperplasia of the adrenal. Note large graafian follicle.

The hyperfunctioning of the adrenal was obvious in this case but the gross and microscopic findings of the adrenals were not striking. This has been reported by others and points to the disparity between excessive function and anatomic changes within the adrenal.[1, 4, 20]

2. Congenital Adrenal Hyperplasia in the Male Sex (Macrogenitosomia Praecox).—Congenital adrenal hyperplasia in the male child may not have any influence on the external genitalia until the child has reached 1½ to 3 years of age. Usually the penis is somewhat enlarged at birth but when

growth does occur it is rapid and the penis and prostate both may attain adult size in early age. The voice becomes deep and other evidences of secondary sex characteristics, such as hair on the pubes, in the axilla, and on the face, also develop early. The excretion of 17-ketosteroids is markedly increased but the testes characteristically remain small and immature. This latter point is of extreme importance in the differential diagnosis of this condition from other endocrine disorders which may give a similar clinical picture.[4] Coincidental with the sexual overdevelopment, somatic growth is accelerated but epiphysial fusion occurs early so that by the tenth year growth may be complete and the patient resembles a short adult with broad shoulders and powerful muscles.

DIFFERENTIAL DIAGNOSIS: Congenital hyperplasia in the male child must be distinguished from (1) virilizing tumors of the adrenal, (2) the neurogenic and constitutional types of sexual precocity, and (3) interstitial cell tumors of the testes.

Virilizing Tumors of the Adrenal: Differentiation from virilizing tumors of the adrenal can usually be made only at laparotomy, although the following facts may lead in the direction of a diagnosis of congenital hyperplasia: (1) the history of occurrence of congenital adrenal hyperplasia in male or female siblings, and (2) the occurrence of adrenal insufficiency or the presence of brownish pigmentations of the skin. The finding of a very high output of 17-ketosteroids, especially the beta fraction, is more common with tumors.

Sexual Precocity: Sexual precocity due to brain lesions, or that arising from idiopathic activations of the pituitary gland occurs at an early age, but the testes grow and mature normally so that at an early age spermatogenesis occurs. The amount of ketosteroid liberation in the urine is also within normal or adolescent ranges. In rare instances, where the testes of a patient with adrenocortical hyperplasia are enlarged, the differentiation may be extremely difficult, but in this type of case it has been found that the testes were enlarged because they were replaced with adrenal cortical tissue.[21] Biopsy of the testes, then, in special cases, is of importance to establish the diagnosis.

Interstitial Cell Tumors: Interstitial cell tumor of the testes is extremely rare and the tumors are usually palpable but may be of oval shape and thus be mistaken for normal testes. Biopsy would establish this diagnosis. In a case reported by Sandblom[22] the 17-ketosteroid excretion was as high as 64 mg. per day.

TREATMENT: As yet there is no effective way of inhibiting the excessive production of the adrenal androgens, but for the male patient the outlook is much happier than for the female patient with congenital hyperplasia because the male patient develops masculine features although he is short and stocky. It may be possible also to delay early epiphysial fusion in certain cases by the use of cortisone. As in the case of the female patients with congenital adrenal hyperplasia special attention must be paid to the psychotherapy of the patient so that he can be eased into his environment with the greatest facility.

CASE REPORT.—I. M. was admitted to the University Hospitals on Feb. 28, 1949, at the age of 26 months, because of increased rate of body growth as well as enlargement of the penis and appearance of pubic hair. At birth the patient weighed 6 pounds, 13½ ounces, and was 51.5 cm. in height. The genitals were reported as being large at birth and pubic hair appeared at the age of six weeks. His growth was rapid so that on admission the child was 99 cm. tall and had the appearance of a well-developed and muscular five-year-old boy (Fig. 6). There was acne of the face, a moderate amount of pubic hair, a markedly enlarged penis and a thickened and wrinkled scrotum. The testes were in the scrotum and they were small. No testicular tumors could be felt. Rectally the prostate was not enlarged. There were no masses in the abdomen.

Laboratory studies showed a hemoglobin of 11 Gm. per cent, leukocytes 10,730 with a normal differential. Blood urea nitrogen was 7 mg. per cent, chlorides 92 meq. per liter and 17-ketosteroid level in the urine, 1.10 mg. per 24 hours (normal is less than 1 mg. per 24 hours at this age).

A diagnosis of hyperadrenocorticism was made and laparotomy advised to rule out a tumor of the adrenal cortex. On March 23, 1949, the abdomen was explored. The right adrenal gland was slightly enlarged, but the left adrenal was markedly enlarged, being two to three times the size of the right gland. No tumors or ectopic adrenal neoplasms were found. The left adrenal was excised. Histologically there was hyperplasia of the adrenal with increased thickness of the zona fasciculata. There was, however, no increase in the fuchsinophilic cells.

Postoperatively, the patient continued to grow at an accelerated rate and the ketosteroid excretion remained markedly elevated (15.3 mg. for 24 hours of urine volume on April 23, 1951).

Comment: This patient was a brother of the female patient with congenital hyperplasia described previously. He did present hyperplasia of the adrenal, but it was primarily unilateral. We have had one other patient in our series who presented a similar picture of unilateral hyperplasia. The excision of the enlarged gland did not seem to have influence on the course of the disease in either patient.

3. SYMPTOMS LIKE THOSE OF ADDISON'S DISEASE IN CONGENITAL ADRENAL HYPERPLASIA.—In both the female and male patients with congenital adrenal hyperplasia, episodes of crisis may be encountered similar to those in Addison's disease. They are characterized by bouts of vomiting, diarrhea, severe dehydration, and a shocklike state. There may be a marked depletion of the serum sodium and elevation of the serum potassium. Death may occur, unless the entity is recognized and treatment instituted. These episodes are most likely to develop in the early few weeks of life and later during acute infections. These acute episodes must be combatted with the use of intravenous salt and glucose solutions as well as the judicious use of extracts of whole adrenal cortex. The response is dramatic and aids in the establishment of the diagnosis. After the acute phase has passed, maintenance doses of desoxycorticosterone, either orally or by implant method, may be required although some patients do satisfactorily with merely a high salt intake. In some patients, as in one of our cases, the difficulty is self-limiting and the patient goes on to an excessive rate of growth with early virilization (Fig. 9). It has usually been assumed that this similarity to the picture of Addison's disease is due to the hyperplasia of the androgenic zone which crowds out the other layers of adrenal cortex concerned in the formation of electrolyes and carbohydrate-

regulating hormones. However, critical studies in this regard, particularly those of Lewis and Wilkins,[26] would indicate that the glyconeogenic hormones are not lacking and perhaps salt loss is due not to a lack of electrolyte-controlling hormones but to a secretion of a type or types of glyconeogenic hormones such as 17-hydroxycorticosterone, which increase the excretion of salt.

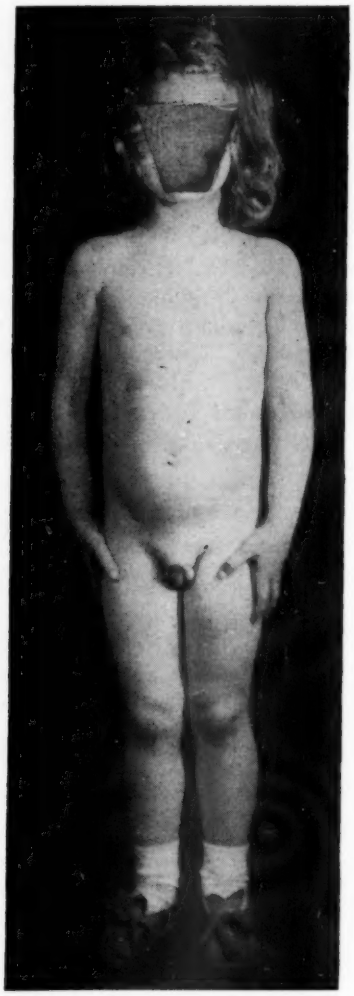


Fig. 9.—A 4-year-old girl with congenital hyperplasia of the adrenal. Note muscular development, pubic and thigh hair, and enlarged clitoris. During the first year of life this patient had several acute episodes of crisis similar to Addison's disease. Treatment with intravenous salt and glucose solutions and extracts of whole adrenal cortex resulted in dramatic response. The patient was placed on maintenance doses of desoxycorticosterone orally for approximately one year after which this drug was no longer needed.

B. *Virilizing adrenal tumors in the female sex:* Excessive androgenic activity of the tumor is characterized by the rapid growth of the clitoris, the appearance of pubic and axillary hair, deepening of the voice, and the onset of seborrhea and acne. Unlike the patient with congenital hyperplasia of the adrenals the external genitalia are normal. The 17-ketosteroid excretion is increased. This output is often greater than that found in adrenal hyper-

plasia and the beta fraction may be increased. These neoplasms are prone to be malignant and may metastasize early to the lungs or bone, or invade the liver.

CASE REPORT.—J. W., a 19-month-old girl, was admitted to the University Hospitals on Sept. 5, 1947, with a history, as obtained from the parents, of inflammation and enlargement of the vulva and clitoris of eight months' duration, appearance of heavy pubic hair, deepening of the voice, increase in body growth and muscular development of six months' duration. At birth and until these symptoms appeared, the child had apparently been normal. Examination on admission revealed a very large and muscular child, appearing to be five years of age (Fig. 10). No masses were felt in the abdomen. The clitoris and labia majora were enlarged and there was considerable dark pubic hair. The blood presure was 140/90. Laboratory examinations revealed the blood and urine to be normal. Blood urea nitrogen was 5 mg. per

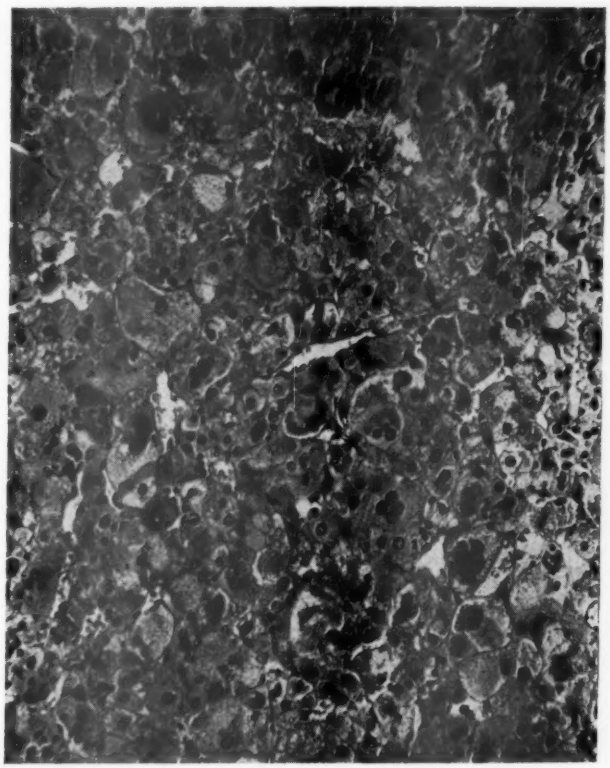


Fig. 10, *A*.—Histologic picture of adenocarcinoma of the adrenal. Note pleomorphism and mitoses.

cent, CO_2 combining power 26 meq. per liter, chloride 100 meq. per liter, serum potassium 3.63 meq. per liter, serum sodium 128.4 meq. per liter. The ketosteroid excretion was 33 mg. per 24 hours (normal less than 1 mg. per 24 hours). Roentgenograms showed advanced ossification of the carpal bones. Intravenous pyelograms and planigrams of the abdomen revealed no masses in the adrenal areas. On Oct. 1, 1947, the patitent was explored transabdominally and a tumor measuring 6 by 4 by 30 cm. was found in the right adrenal. The left adrenal appeared normal. The entire right adrenal with its accompanying tumor was removed. Histologically, the tumor proved to be an adenocarcinoma of the adrenal cortex (Fig. 10, *A*). Ponceau-fuchsin stains of the tumor showed focal collections of fuchsinophilic cells, as did the normal adrenal tissue, indicating the possibility of concomitant adrenal hyperplasia. Postoperatively, the patient did very nicely but subsequently developed a ventral hernia which was

repaired eight months after the original operation. At that time, the right adrenal was re-explored and no recurrences noted. In three and one-half years after surgery there was no evidence of recurrence. The patient has become much more feminine in her play and habits and is no longer growing at an excessive rate. Repeated 17-ketoteroid excretion levels of the urine have remained between 1 and 1.5 mg. per 24 hours (Fig. 11).

COMMENT: The coincidental appearance of adrenal hyperplasia and virilizing tumor in this patient is extremely interesting. A detailed study of female patients with virilizing tumor or with hyperplasia is indicated, to determine if other similar cases have been encountered. It may possibly be that adrenal hyperplasia is a precursor of adrenal adenocarcinoma.

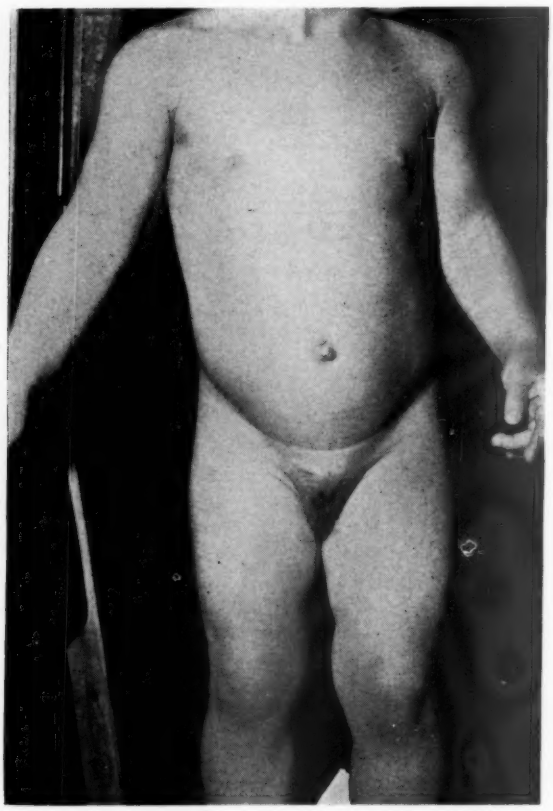


Fig. 10, *B*.—Preoperative picture of patient with adenocarcinoma of the right adrenal. Note muscular development and pubic hair.

II. *Cushing's Syndrome*.—This syndrome is characterized by increasing obesity of a "buffalo variety," i.e., deposition of fat about the shoulders and face, weakness, purple striae of the abdomen, increased capillary fragility, osteoporosis, hypertension, virilization of the female, diabetic sugar curve, increase in serum sodium and decrease in serum potassium. There is increase in urinary excretion of both 11-oxysteroids and 17-ketosteroids. In children there are evidences of sexual precocity but they are not as marked as in congenital hyperplasia.

Pathogenesis: Thompson and Eisenhardt[27] studied 98 cases that came to autopsy and showed that basophil adenoma of the pituitary gland was found in approximately 60 per cent and adrenal tumors in 22 per cent. It is generally agreed that the symptoms of the Cushing's syndrome, with or without pituitary tumors, are due to excessive production of the hormones of the adrenal cortex. As in other endocrine syndromes, the primary disorders initiating the hypersecretion may be in the hypothalamus, pituitary, or in the

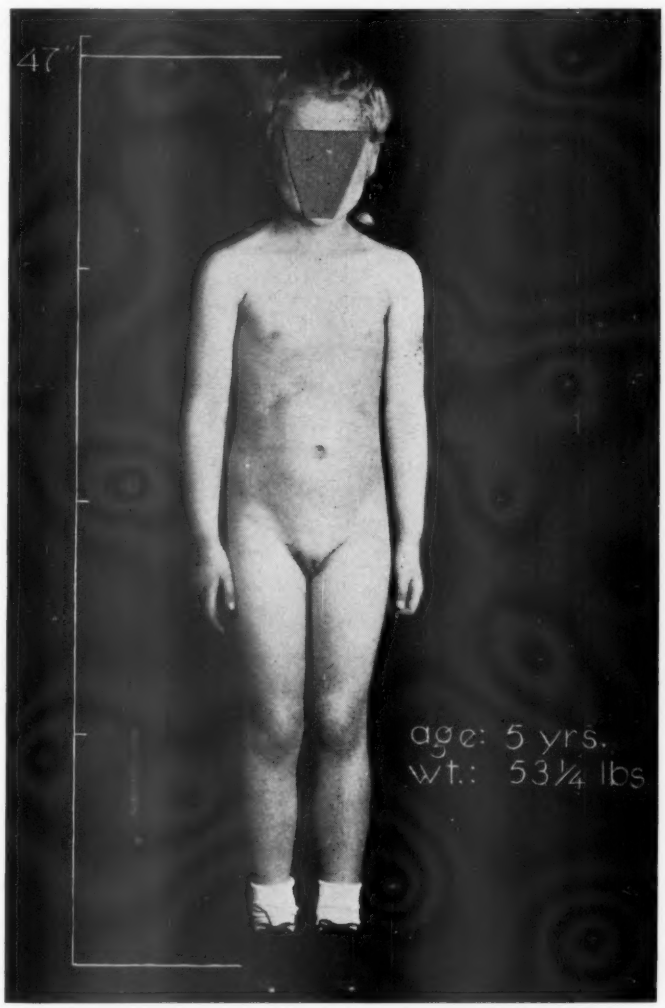


Fig. 11.—Photograph of a patient taken approximately three years after removal of adenocarcinoma of the right adrenal. The rate of growth has become normal and she is now feminine in her habits. The deep voice and a few elongated coarse pubic hairs remain unchanged.

"target gland" that is, the adrenal itself. The changes in the basal cells of the pituitary described by Crooke[28] and found uniformly in Cushing's syndrome, are felt by many to be the results of hypersecretion of the adrenal rather than the cause of it. Wilkins[4] states that all cases of Cushing's syndrome beginning before the age of eleven years are due to adrenal tumors.

Treatment: When the Cushing's syndrome is due to adrenal tumor its removal results in reversion to normal on the part of the patient. When adrenal hyperplasia occurs, the treatment of Cushing's syndrome is usually unsatisfactory. Radiation of the pituitary gland and the use of testosterone and estrogens to combat osteoporosis have been advocated. In cases where high serum sodium and low potassium are found, a diet low in sodium and the administration of potassium chloride may be indicated. From the surgical point

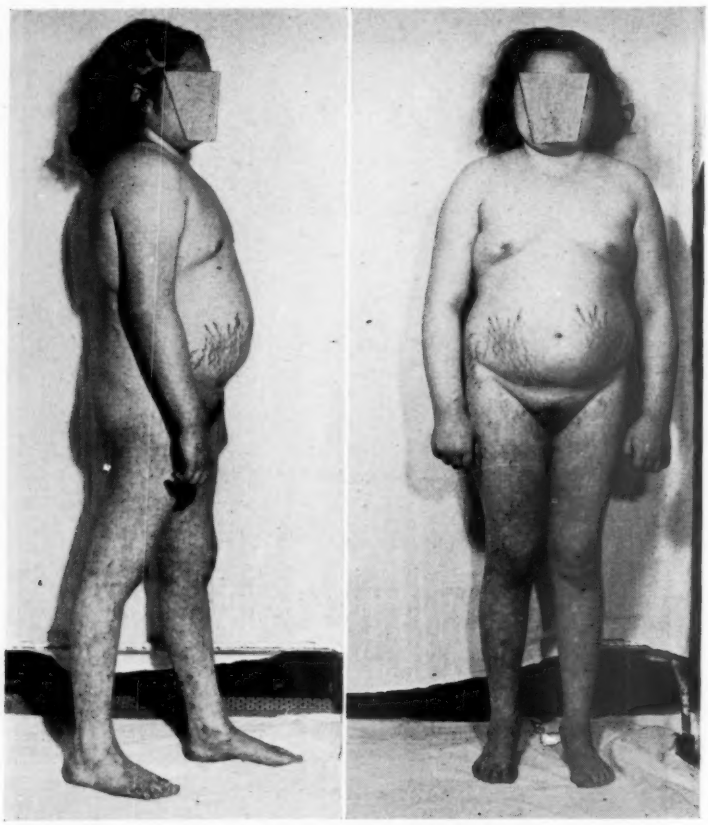


Fig. 12.—A 13-year-old girl with a typical picture of Cushing's syndrome. Note the "buffalo" type of obesity, striae of abdomen and discoloration of lower extremities. The external genitalia were normal. Blood pressure was 184/124 and 17-ketosteroid excretion 19 mg. per 24 hours.

of view, the removal of one adrenal gland has usually resulted in little change but we have encountered one patient who had an excellent result following unilateral adrenalectomy (see Case Report which follows). The group at Mayo Clinic[29] have performed bilateral subtotal adrenalectomy in three patients with appreciable improvement.

CASE REPORT.—M. H., a thirteen-year-old white girl, was admitted to the University Hospitals on Feb. 16, 1944, complaining of rapid weight gain and obesity, particularly of the face and shoulders, of about three years' duration. Examination revealed a short, obese female child of about thirteen years of age, with the obesity most marked about the shoulders and face (Fig. 12). Her facial obesity was so marked that both eyes were mere slits. The blood pressure was 184/124 and there were purple striae over the lower abdomen. The ex-

ternal genitalia were normal for her age. Laboratory data revealed occasional traces of sugar in the urine, normal hemogram, normal serum CO_2 combining power, potassium, and sodium levels. The 17-ketosteroid excretion was 19 mg. per 24 hours (normal 3 to 5 mg. per 24 hours). X-ray examinations of the skull showed only demineralization, and funduscopic examination was negative. Bilateral pneumoadrenograms were done and were interpreted as showing questionable enlargement of the left adrenal. On March 21, 1944, the patient was explored transperitoneally and both adrenals were visualized. The right appeared normal,

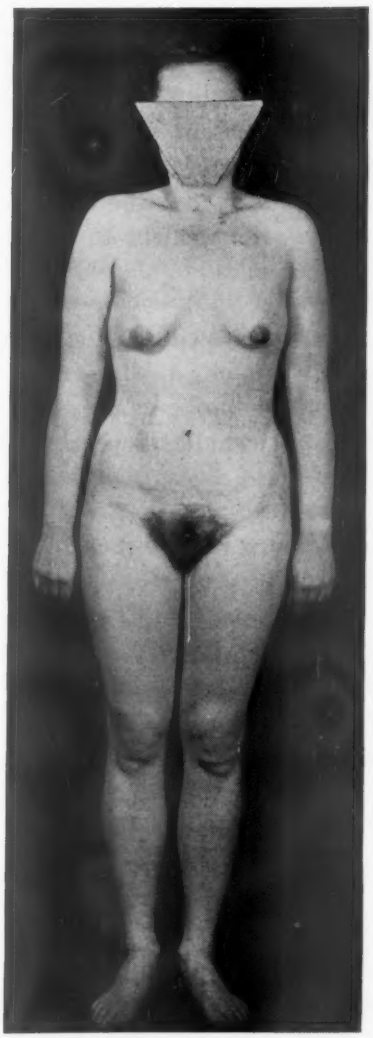


Fig. 13.—Photograph of patient shown in Fig. 12, taken Dec. 26, 1951. Body configuration is now normal. The patient does have residues of the striae on the abdomen and thighs. They are now white. Serum CO_2 combining power, sodium, and potassium are normal, glucose tolerance test shows a normal curve, 17-ketosteroids in the urine are 2 mg. per cent, blood pressure is 120/90 mm. Hg.

but the left was felt to be slightly enlarged and was removed.* Penceau-fuchsin stains showed adrenal hyperplasia. The postoperative course was complicated by the development of a left subphrenic abscess which was drained posteriorly. Following her recovery from surgery her condition improved gradually but markedly. She lost her obesity, striae and hypertension. Recent checks (May, 1950, and December, 1951) showed her to be essentially normal without any evidences of Cushing's disease (Fig. 13).

*By Dr. C. Dennis.

COMMENT: The dramatic response of this patient and the favorable response of the patients treated by Kepler and co-workers at the Mayo Clinic[29] by bilateral partial adrenalectomy would indicate that further attempts at correction of this condition by removal of one or portions of both adrenals is in order. Particularly is this true now that substitute adrenal therapy for these patients is better understood and more potent hormones are available.

III. *General Comments Concerning Localization and Removal of Adrenal Cortical Tumors.*—The localization of the tumor may be difficult when it is not palpable. A flat plate of the abdomen may show calcification in the region of the tumor. Planigrams are helpful and should be done in all cases. Pyelograms may show abnormal displacement of one kidney by an overlying mass. Cahill[30] advocates injections of air into the perirenal space, but this procedure is not without danger and results are frequently inconclusive. Whenever clinical and laboratory findings are sufficient to suggest an adrenal tumor, provided the patient is in the best possible shape, laparotomy should be carried out.

The preoperative preparation of the patient is extremely important and diagnostic tests should be carried out to determine the possibility of latent adrenal insufficiency. Thorn and his co-workers[31] have shown that normally a decrease of 50 per cent in the circulation eosinophils and a rise in urinary uric acid follows the injection of 25 mg. purified ACTH, intramuscularly. When the eosinophils do not decrease, or the drop is less than 50 per cent, overt or latent adrenal insufficiency must be seriously considered.

The electrolytic pattern of the serum, particularly the concentration of sodium and of potassium should be carefully checked. In adrenal insufficiency the serum sodium is decreased and potassium increased. However, in less severe states, levels of those ions in the blood may be normal although the intracellular concentration may be abnormal. Where latent adrenal insufficiency is considered the Robinson-Power-Kepler diuresis test should be carried out.[32]

To prevent acute adrenal insufficiency from appearing throughout operation or immediately following removal of the adrenal gland or a cortical tumor, the patient should be given glucose and salt solutions previous to the operation and in addition, 10 c.c. of cortin (whole adrenal cortical extract) should be given intramuscularly the night before surgery and in the morning prior to sending the patient to the operating room. An intravenous drip containing glucose and saline solutions should be started at the time of operation and an anesthetic agent should be used which does not depress the adrenal function. In the main, we have used Pentothal Sodium-curare mixtures with intratracheal oxygen. Prior to opening the peritoneal cavity 10 c.c. of adrenal cortex extract are given intravenously and as the adrenals are explored, if any pathology is found in one gland, the other should be carefully looked at before any extirpation is done. If the opposite gland is atrophic or absent, then portions of the involved gland should be left, if at all possible. If this is not possible, adrenal insufficiency should be anticipated and treatment carried out immediately.

Treatment of acute adrenal insufficiency[4]*:* Intravenous salt, glucose, and whole blood should be given. Adrenocortical extract, in doses of 1 c.c. per kilogram of body weight, should be given intravenously, and, at the same time, 5 to 10 c.c. should be administered intramuscularly. If there is no response, these doses should be repeated in 20 to 30 minutes. During the first 24 hours, intramuscular injections of adrenocortical extract should be repeated every three hours in doses of 5 c.c. for small infants, 10 c.c. for older infants and 30 c.c. in adults. Salt and glucose solutions should be continued by intravenous drip in amounts as usually calculated in relationship to the patient's weight. Adrenalin may also be given intravenously in doses of 0.5 c.c. in 1:1000 solution to combat hypotension. A favorable response to therapy is manifested by return of the pulse and blood pressure to normal levels, restoration of the weight loss, correction of hypoglycemia, and return to normal of the pattern of serum electrolytes. Treatment with adrenocortical extract should be continued for two or three days and then gradually decreased. In acute adrenal crisis, desoxycorticosterone should never be given alone[4] instead of adrenocortical extract, as it may cause excessive retention of salt, leading to cardiac failure.

Surgical approach: The standard surgical approaches to the adrenal are (1) extraperitoneal nephrectomy incision, (2) the longitudinal lumbodorsal incision, (3) the transperitoneal approach through either a transverse or vertical incision of the upper abdomen, and (4) the transpleural route. In our cases the transperitoneal approach has been preferred because it affords visualization of both adrenals as well as the entire abdominal cavity to rule out the possibility of ectopic adrenal tissue. This incision also permits better visualization and clamping of the vessels to the adrenals before manipulation or removal of adrenal neoplasms. The abdominal incision should be closed with interrupted stitches of nonabsorbable sutures. Possibly steel sutures are the best in this regard, for these patients have a tendency toward infection and their wounds do not heal kindly or readily. This is interesting in light of the experimental evidence to indicate the depressing action of cortisone upon wound healing[33] in experimental animals.

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In Memoriam

Barney Brooks
1884—1952

Dr. Barney Brooks, Professor of Surgery, Vanderbilt Medical School, died at the age of 67 in the Vanderbilt Hospital, March 30, following a cerebral hemorrhage. Dr. Brooks was born in Jacksboro, Texas, in 1884. He graduated from the University of Texas, Austin, in 1907, and received his medical degree from The Johns Hopkins Medical School, Baltimore, in 1911. After serving an internship in surgery in The Johns Hopkins Hospital, 1911-1912, under Dr. W. H. Halsted, he went to the Barnes Hospital, St. Louis, when the Washington University School of Medicine was reorganized. He was assistant resident, then resident, in surgery in the Barnes Hospital, 1912 to 1916. He was appointed to the faculty of Washington University School of Medicine as instructor in surgery in 1916 and rose to the rank of Associate Professor of Surgery by 1924. He was assigned as a teacher of surgery to Washington University during World War I, held the rank of Major, Reserve Corps, United States Army, and was Commanding Officer of Surgical Hospital Number 4, United States Army.

He became Professor of Surgery in the Vanderbilt Medical School and Surgeon-in-Chief to the Vanderbilt Hospital in 1925, and served in that capacity until 1951, when he asked to be relieved of administrative duties and became Professor of Surgery, Emeritus.

His many scientific contributions included work on growth and regeneration of bone, intestinal obstruction, disease of joints and of blood vessels, surgery of the gall bladder, carcinoma of the mammary gland, surgery in old age, and effects of temperature on wounds.

His accomplishments in the field of education are reflected in the number and excellence of the distinguished surgeons who have had their training under him, many of whom occupy important teaching and research positions throughout the country, as well as in the many hundreds of graduates who testify to his excellence as a teacher.

Dr. Brooks was past president of the Southern Surgical Association and the Nashville Surgical Society. He has been an Associate Editor of *Annals of Surgery* and a member of the advisory council of the publication Surgery. He was a member of the American Medical Association, the Southern Medical Association, the Society of University Surgeons, the American Society of Clinical Surgery, the American Board of Surgery, the International Surgical Society, the American College of Surgeons, Alpha Omega Alpha, and Sigma Xi.

Dr. Brook's death removes from Vanderbilt one of the outstanding medical teachers of our time and one of those responsible for the Vanderbilt Medical School's high standing in medical education during the last quarter of a century.

Book Reviews

Lumbar Puncture and Spinal Analgesia. By R. R. Macintosh, M.A., D.M., F.R.C.S.(Edin), D.A., Nuffield Professor of Anaesthetics, University of Oxford, Civilian Consultant in Anaesthetics, Royal Air Force, Examiner for the D.A., Anaesthetist, United Oxford Hospitals, Fellow of the Faculty of Anaesthetists, Royal College of Surgeons. Pp. 149, with 111 illustrations. Baltimore, 1951. Williams and Wilkins Company. $4.50.

The purpose of this little monograph is graphically and verbally to demonstrate the techniques of performing a spinal puncture and of administrating a spinal anesthetic agent. The illustrations are excellent and instructive. There seems to be a great deal of repetition in the drawings, but this adds to their instructive value.

The first chapter is a brief outline of the history of spinal puncture and spinal anesthesia. The next three chapters are concerned with the anatomy of the vertebrae and spinal cord. They are rather elementary but, along with the succeeding chapters on the technique of performing a spinal puncture, they certainly carry out the author's intent of teaching the beginner the essentials of this procedure. There is a chapter on the distribution of anesthetic solutions. It is inconclusive and leaves the impression that the author is interested only in Nupercaine. The dangerous circumstances connected with barbotage of spinal anesthetic agents is not mentioned. The chapters on Headaches, and on Do's, Don'ts, and Doubtfuls are sketchy and brief—too brief for the relative importance of these subjects in clinical medicine. However, in such a small monograph it is obvious every aspect cannot be included.

This reviewer believes that the author has accomplished in good order a necessary task in medical instruction and that this book can be of value not only to the inexperienced but also to the expert.

Clinical Unipolar Electrocardiography. By B. S. Lipman, A.B., M.D., Assistant in Medicine, Emory University School of Medicine, Atlanta, Georgia, and Edward Massie, A.B., M.D., F.A.C.P., Assistant Professor of Clinical Medicine Washington University School of Medicine, Director of Heart Station, Barnes Hospital, St. Louis,. Pp. 232, with 191 illustrations. Chicago, Ill., 1951, Yearbook Publishers. $5.00.

This book is a good outline of the fundamentals of unipolar electrocardiography. The basic concepts of unipolar electrocardiography are presented in a clear, concise, and simple manner together with numerous diagrams. Because of the authors' attempt to make things simple, they make many dogmatic statements which, as yet, have not been entirely accepted by all clinical electrocardiographers. However, they do state from the outset that the data are a composite of lectures that are given to the medical students and therefore would tend to be more dogmatic.

In the chapter on the physiologic principles, the authors decry memorizing certain patterns and various clinical syndromes that are aided in diagnosis by the electrocardiogram. However, in the succeeding chapters, the word pattern is used repeatedly to describe such things as a myocardial infarct, left bundle branch block, ventricular strain, etc. Also there are no examples or explanations of the various arrhythmias.

In summary, the authors have explained and presented, with excellent examples, the current data on clinical unipolar electrocardiography. Except for the two weaknesses mentioned above the book is a good text for anyone whose experience with electrocardiography is limited.